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BULLETIN ON NARCOTICS

Vol. V, No. 4 OCTOBER-DECEMBER 1953

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Bulletin on NARCOTICS

Vol. V, No. 4, OCTOBER-DECEMBER 1953

UNITED NATIONS

DEPARTMENT OF SOCIAL AFFAIRS

New York

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Table of Contents

	Page
GENERAL	
Clandestine heroin laboratories, by C. Vaille and E. Bailleul	1
Fighting the illicit traffickers, by George H. White	7
Death from therapeutic doses of morphine or morphine-scopolamine in persons affected by alcohol or barbituric acid, by Professor Knud O. Møller	11
TECHNICAL	
The physical methods for the identification of narcotics	20
Part IA. Introduction to identification of narcotics by physical methods, by Charles G. Farmilo and Leo Levi	21
Stereochemistry of morphine, by David Ginsburg	32
OFFICIAL	
New Peruvian legislation on cocaine manufacture	47
BIBLIOGRAPHY	
Scientific publications on narcotic drugs for 1952	50

Clandestine Heroin Laboratories

By C. Vaille and E. Bailleul

Mr. Charles Vaille, Chief of the Service Central de la Pharmacie of the Public Health and Population Ministry of France, has been for several years the delegate of France at the Commission of Narcotic Drugs; he is now the Vice-President of this Commission and was Chairman of the Main Committee of the United Nations Opium Conference. Mr. Edmond Bailleul, Commissaire divisionnaire *of the Sûreté nationale, has taken a most important part in the successful campaign waged in France during the last two years against the illicit traffic in narcotic drugs.*

Since the end of the Second World War there has been a considerable increase in the illicit use of narcotic drugs in the world and a correspondingly large increase in the number of traffickers and of clandestine laboratories for the manufacture or conversion of dangerous narcotics.

In many countries the police have discovered and put out of action clandestine laboratories established for the purpose of processing either opium or, more often, raw morphine, which is converted into heroin.

There is a greater demand for the drug in this latter form and it fetches the highest prices on the illicit market, compressed as it is into a small compass which enables it to be easily hidden in transit both in the countries through which it passes and in those where it is processed and consumed. Moreover, this drug can be adulterated to a greater degree than any other and therefore constitutes the most profitable traffic.

Lastly, raw morphine can be refined and converted into almost pure heroin (90 to 97 per cent) with relatively simple means and material, with the help of products the sale of which is uncontrolled, and without the need for any special adaptation of the premises used; in this way many kilos can be produced weekly.

A bathroom or kitchen fitted either with town gas or butane gas or with electricity is sufficient for the purpose.

France, where there are happily few drug addicts, is a transit country because of its geographical situation. The raw materials are easily imported clandestinely by its Mediterranean coast, while its Atlantic coastline forms a natural exit for exports to the American countries.

Its situation has also led to its becoming a converting country, as is proved by the successive discovery of five clandestine laboratories on its territory in a little over a year by the special services of the French police.

The French police services, on the instructions of the Central Office, have concentrated on the discovery of clandestine laboratories, with the object of stopping the illicit export traffic at the source.

This activity calls for complete co-ordination of the preventive services of the territories of the whole French Union, within the framework of the legal provisions, and demands from the officials who take part in it incessant and often thankless labour for which great professional competence is required.

Among the five cases mentioned above which led to the discovery of clandestine laboratories, two inquiries in particular throw light on the great efforts required of the members of the special police. One of them took place at Marseilles by the combined efforts of the Algerian police services and the Marseilles judiciary police services; the other was carried out at Paris and Montgeron, which is about thirty kilometres from the capital, by the preventive group of the Central Office.

Pinori case, Marseilles

Following the arrest at Algiers of two traffickers, Pierre Cardi and Jules Ignace, both seamen and traffickers in heroin, the North African and French police services carried out a joint action at Marseilles in April 1952. The object was to discover the source of a large traffic in heroin being carried on between this port and North Africa.

The first information gathered seemed to show that a trafficker, known simply as "Roger", an ex-sailor on a North African line, was one of the persons chiefly concerned in this traffic, which originated in the Joliette quarter of Marseilles.

One of the seamen whom the police already suspected of engaging in the narcotics traffic was Roger Legent, who lived at 20, rue Plumier, in the Joliette quarter. A constant watch over his movements was immediately instituted.

On 18 April 1952, at 8.30 a.m., Legent, after waiting for a few minutes near the house where he lived, met a North African with whom he must have had an appointment. After a short conversation with this man, Legent went into a nearby bar to telephone. One of the detectives who were watching him followed him there and heard him ask for "3" to be delivered at the usual meeting-place.

By constantly shadowing Legent the police saw him receive a packet from a man driving a Ford-Vedette car, whose registration number was taken.

Legent was immediately arrested and was found in possession of an unopened packet containing 300 gr. of heroin in cellophane bags. He refused to give his purveyor's name.

The appearance of the driver of the car and even the type of car showed that large-scale traffic was involved. It was therefore decided not to arrest the driver but to watch him closely.

As the registration number of the car was known, the owner and the driver were easily identified. The driver was one Vincent Pinori, aged 37, living at Marseilles, who called himself a carrier but in fact had no definite occupation.

Pinori was followed and watched day and night for several weeks. It became evident that he was a regular customer of the bars frequented by the known traffickers and had appointments there, yet he seemed to live apart from the usual circle of the Marseilles drug traffickers.

While shadowing Pinori the police officers saw him enter a building at 42, rue d'Aix, which was occupied by a number of tenants. He returned there a few days later and the detective who was following him was adroit enough to see which bell he rang. It was that of an apartment on the second floor at the back of the house, rented by Mr. Sauveur Tranchini.

Pinori's visits to 42, rue d'Aix, became more and more frequent and lasted longer, and the police officers came to the conclusion that there must be a clandestine laboratory there.

That being so, they arranged with the Public Prosecutor's Department at Marseilles to begin legal proceedings and on 21 July 1952 a rogatory commission was set up for the purpose of taking any action that might reveal the facts.

On 22 July Pinori arrived at the rue d'Aix early in the morning, left the building at the end of the morning and returned there at about 2.20 p.m. Apparently, therefore, he was hard at work and the police decided to take action.

At 3.30 p.m. the police officers went to Tranchini's apartment. After making the usual demand for admission, they were obliged to break in the door, there being no reply from within.

There they found Pinori and a person of the name of Alexis Carcassone, aged 28, a cousin of Tranchini, who had left him in charge of the apartment. The kitchen of the apartment had been fitted up as a laboratory. There were a number of containers full of morphine, as well as the apparatus, instruments and products needed to purify morphine and to convert it into heroin. The containers gave off a characteristic acetic smell.

Carcassone readily admitted that he was aware of the nature of Pinori's activities and that he had given the latter permission to use the apartment left in his charge by his cousin Sauveur Tranchini.

Pinori, having been caught in the act, was unable to plead innocence, but he gave the most preposterous explanations regarding the source of the morphine. There is no doubt that he intended to extend his trafficking, for during the search which followed a complete list of supplies for fitting up a larger laboratory was found.

He admitted that on 18 April 1952, as described above, he had handed Legent a packet, of the contents of which he claimed to be ignorant and which he said had been entrusted to him.

The truth is that the heroin delivered on that occasion came direct from Pinori's clandestine laboratory. He had decided to dispose of the narcotics he manufactured by exporting them to North Africa through men like Roger Legent, a seaman who served on the lines going to Algeria.

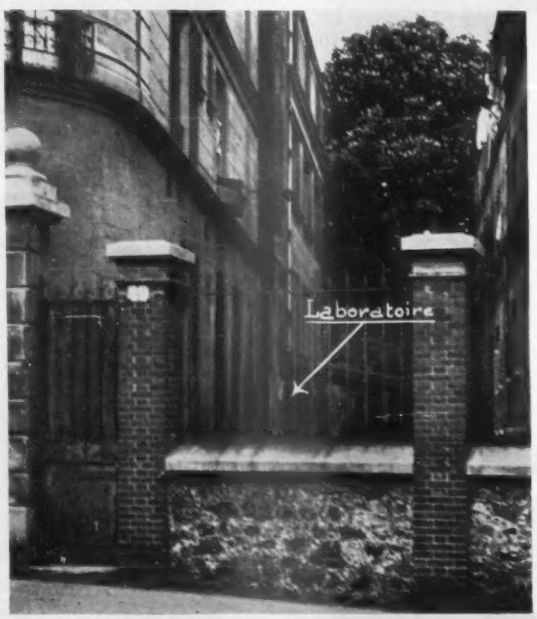
Pinori evidently had a large demand to meet, probably greater than that constituted by the North African market, since he was planning to expand his capacity for clandestine production.

In this operation the judiciary police of Marseilles seized six kilogrammes of narcotics in course of conversion.

Thus through the co-operation of the Algerian and French police forces and the co-ordination of their efforts an important source of narcotics for the external market was suppressed. Pinori's laboratory was capable of producing about four kilogrammes a week.

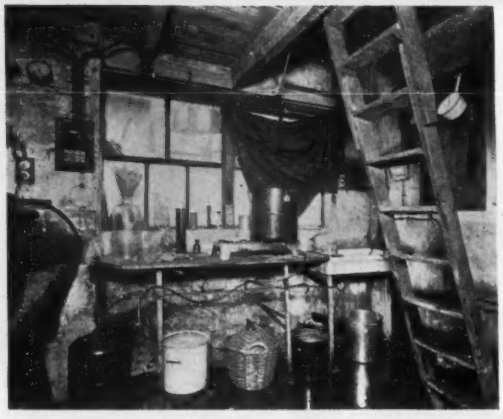
Montgeron Case

Acting on detailed information received, the Special Branch of the Préfecture de Police in Paris made a rapid raid on 18 March 1952 and found in a weighing-machine repair shop at 29, rue des Envierges, Paris (20), a clandestine laboratory in full operation, installed and run by one Auguste Salgues, aged 44.



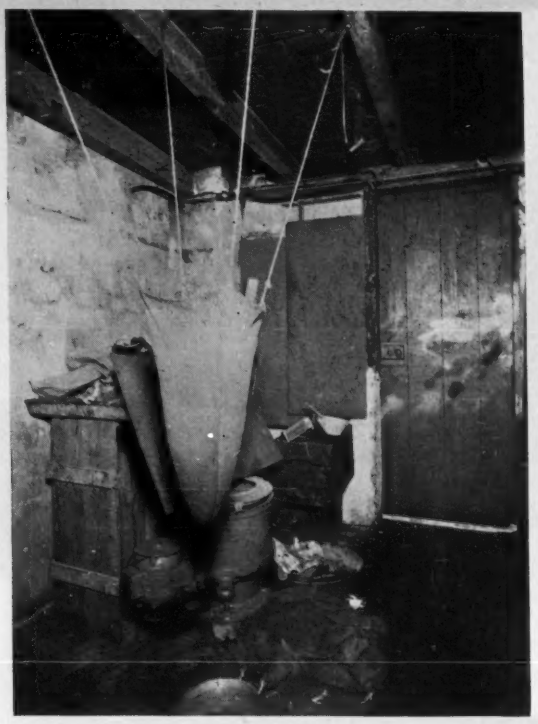
Gate of the laboratory yard at Montgeron

Main pieces of apparatus



Laboratory proper

Dishes of morphine at various stages of purification



Waste-material room

During the subsequent investigations a detective attached to the Central Office was informed that a certain "Marius", who frequented a bar in the 20th *arrondissement* of Paris, had been implicated in Salgues' activities, if not directly at least so far as the narcotics traffic was concerned.

This detective let it be understood in the quarter that he was a shopkeeper looking for suitable premises; he discovered the man in question, who called himself Marius Reversac, described himself as a chemist and lived in the Impasse du Progrès. He contrived to make his acquaintance and thenceforth Reversac was followed and his every movement was watched by the police.

By shadowing him it was established that he was in frequent touch with a woman who owned a Peugeot car and who was identified as one Marie Poteau, aged 34, living in an apartment at 35, rue Bonnet, Paris (18) with one Marius Meysson, aged 42, who had received several prison sentences.

A watch was also placed on this woman and her lover. Owing, however, to traffic difficulties and to the skill with which she drove her car, the trail was lost on several occasions, and especially one Friday evening, when she and Meysson were going towards the southern suburbs of Paris. Contact was not re-established until the following Tuesday.

On the morning of 26 May Marie Poteau's car, followed by the detectives, led them to the salesrooms of a company which specialized in the manufacture and sale of laboratory products and apparatus.

With the help of Reversac, who was with her, Marie Poteau took delivery of a number of parcels and took them by a roundabout route to Montgeron, a place in the Seine-et-Oise *département*, thirty kilometres from Paris, where she drove her car into the garden of an isolated house, the Villa Castelran, registered as the property of Meysson's father, who lives at Marseilles.

It was very difficult to watch this villa, owing to its isolated situation on an unfrequented road, which meant that any police officers who constantly shadowed the persons concerned would rapidly be detected. Nevertheless, it was essential to do so, for it transpired that Poteau and Meysson spent every weekend there.

A search was therefore made for an observation post where the detectives could be installed with a wireless transmitter so that they could communicate information about the movements of the inmates of the villa and their visitors, and whence they would be able to take photographs with a telelens.

It should be observed that the Villa Castelran is situated beside the Paris-Lyons railway line, which has recently been electrified.

A team of detectives therefore visited an old man living on the ground floor of a near-by house, about eighty metres from the villa. They stated that they were broadcasting officials and that they were trying to find out the causes of interference in wireless reception from the newly electrified line. They secured the loan of a room, where they installed their material. Two teams of two detectives each took turns in keeping watch, keeping in touch by wireless with a police station about five kilometres away, on the road to Paris.

They notified arrivals and departures by means of a pre-established code and warned police cars stationed on the roads from the villa, which were thus able to shadow the cars indicated to them and to note their descriptions and numbers.

In this way a number of visitors to the villa were identified and card-indexed by the Central Office.

After spending four days at the villa, Marie Poteau and Meysson left by car at about 9 a.m. on 17 June. One of the police cars stationed near-by was informed by radio and managed to follow them to another villa at 8, allée de l'Alma, Perreux (Seine), the residence of a certain Marius Ansaldi, who was well known to the Central Office and was suspected of being one of the principal drug-traffickers to the United States of America, though he had never been arrested or convicted on that count.

Between 17 and 20 June, Marie Poteau and Meysson made more journeys to the villa, taking numerous packages, and accompanied by another man whom the police identified as Don Joseph Franchi, aged 57, and who had been implicated in a case of drug-trafficking in 1932.

On the night of 22 June, convinced that a clandestine laboratory was operating in the villa, the chief of the Central Office and one of his assistants made a detailed survey of the points of access to the villa, by going around the outer limits of the property. It was a warm night and near the garage the two men noticed a strong acetic odour. Later they found that a pit had been dug in the garden, at the foot of the surrounding wall, and that the laboratory drains led there instead of running into the sewers.

On 24 June, Poteau, Meysson and Franchi again visited Ansaldi at Perreux; he accompanied them to Paris, to the normal residence of Meysson in the rue Bonnet.

On 27 June, Don Joseph Franchi placed two demijohns in Marie Poteau's car, which was parked near her home; he then went with her to the same chemical supplier whom she had previously visited with Reversac. They were handed several packages and then returned to Poteau's home, leaving the packages in the car.

Towards 11.30 a.m., Marie Poteau, accompanied by Meysson, Franchi and Ansaldi emerged from the house in rue Bonnet and more packages were loaded into the car, which was driven away a few minutes later by Poteau, with Ansaldi as the only passenger; she drove him to a building at 49, rue Caulaincourt, and he went in. He came out a few minutes later, carrying a small brown leather suitcase with a strap round it, the exact description of which was noted by a detective. The suitcase was placed in the boot of the car, which returned to the rue Bonnet, whence Poteau, Meysson and Franchi left for Montgeron, leaving Ansaldi in Paris.

All these scenes were telephotographed, with the exception of the episode in the rue Caulaincourt, where unfortunately a delivery van blocked the field of vision.

From then on the investigators were certain that the clandestine laboratory was run by Marius Ansaldi and that he supplied the raw morphine and disposed of the processed heroin.

A permanent guard was put on duty to take immediate action should Ansaldi return to the laboratory.

Apart from putting the laboratory out of production, it was considered essential to catch Ansaldi red-handed, for he was one of the leading drug-traffickers and had so far escaped the police.

At 11.38 a.m. on Sunday, 29 June, the inspector on duty gave the prearranged code signal indicating that Ansaldi had arrived at the Villa Castelran. The plans were immediately put into operation, the villa was surrounded, and at noon precisely the police broke in.

Marius Ansaldi, Meysson and Franchi were caught in the garage, the entrance of which from the garden was concealed by the car, amidst a considerable amount of equipment used to purify crude morphine and convert it into heroin. It was fully equipped as a laboratory and was amply stocked with chemical products and apparatus, including an electric vacuum pump and an electric pulverizer.

With the exception of the kitchen and two bedrooms, the whole villa and its outbuildings were

used for the conversion of morphine into heroin and its handling and packing. A second laboratory and a drying-room for the morphine had been installed on the second floor and three kilogrammes of morphine in process of conversion were found there.

The suitcase that Ansaldi had fetched from the rue Caulaincourt was lying on a pile of filters in the dining-room, near a pair of scales. From the state of its interior fittings it was evident that it had been regularly used for this kind of transport.

At 7 p.m. Ansaldi's residence at Perreux was searched in his presence.

In a drawer in his bedroom were found the keys of the flat in the rue Caulaincourt from which he had fetched the suitcase containing the crude morphine. Chemical products used to purify morphine were found in the cellar.

The residence of Poteau and Meysson was also searched; in addition to some laboratory instruments, papers and invoices were found which established that Meysson had been engaged in these activities since the beginning of 1951 at least.

Marius Reversac, arrested on 30 June, was identified as being in reality Auguste Marius Morganti, known as "Marius", who had been sentenced by the Grenoble Assize Court on 3 November 1935 to hard labour for life, on a murder charge.

During interrogation, Meysson admitted that he was the chemist, and Franchi his assistant, but refused to give any information concerning his earlier activities.

Ansaldi merely admitted the facts that had been established by the investigators and refused to reveal the source of the crude morphine.

Three kilogrammes of morphine, a considerable amount of laboratory equipment and products used in the conversion of morphine were seized in this operation, as also the car which had been used for transport. In addition, five automatic pistols and some Swiss watch movements (the latter having been smuggled into the country by Franchi) were found during the searches.

The successful conclusion of this long investigation put out of operation a clandestine laboratory which was equipped to produce several dozen kilogrammes of heroin per month, though that production was naturally limited by the supplies of crude morphine available.

During the 115 days preceding the arrests, the staff of the preventive group from the Central Office, the inspectors, drivers and photographers, were on duty for an average of seventeen hours a day and by extraordinarily good luck not one of them was noticed or detected by the persons whom they were constantly watching or following.

CONCLUSIONS

There are several possible explanations for the appearance on French soil of numerous clandestine heroin laboratories. They are based on the following facts:

(1) *Route followed by the traffic*

Opium originating in the Middle East and smuggled to North America usually passes through the French, Italian and Spanish ports on the Mediterranean, and across the Atlantic on the way to the ports on the eastern shores of the United States of America (see document E/CONF.14/9 of 19 March 1953 of the Economic and Social Council).

(2) *Increase in seizures in France*

The quantities of opium seized in France, by year, were approximately as follows:

Year	*Kilogrammes*
1946	10
1947	11
1948	20
1949	19
1950	44
1951	355

The quantities seized increased steadily in the post-war years, reaching a maximum in 1951. There is no doubt that this is only partly due to the tightening of controls. Marseilles was the principal port of entry for illicit opium from the Balkans, Turkey and Iran.

(3) *Situation in Italy*

After the war, an extensive illicit traffic in narcotic drugs was organized in Italy and has been one of the main sources of supply for the United States. In 1950, the efforts of the Italian police resulted in the discovery of one of the principal sources of the traffic. The police continued their endeavours and succeeded in uncovering the scandalous conduct of an employee of a well-known Italian chemical firm who, under cover of the legal manufacture of codeine, was actually manufacturing hundreds of kilogrammes of heroin, which was sold on the illicit market.

(4) *Control in opium-producing countries*

In 1949-50 one of the largest opium-producing countries imposed very strict control measures on the raw materials used to purify the morphine extracted from opium and to manufacture heroin. While such a control was possible in that country, which was administratively well organized but industrially little developed, it is virtually impossible in a highly industrialized country such as France.

(5) *Increased international co-operation*

Since the end of the war, the annual meetings of the United Nations Commission on Narcotic Drugs have, among other things, brought together the officials responsible for the control of narcotic drugs in the various countries; the result has been an increase in international co-operation between police forces in the campaign against illicit traffic in narcotic drugs.

* * *

To sum up, since about 1950, part of the illicit traffic of Mediterranean origin has shifted to France. This is reflected, on the one hand, in the increase in

seizures and, on the other hand, in the discovery of numerous clandestine laboratories, and is accounted for by the geographical situation of France and by the blow dealt to illicit traffic in Italy.

It would appear that in most cases crude morphine is prepared in the country of origin, in order to facilitate transport. For obvious reasons of convenience, to disperse the risks and to increase their own profits, the gangs of traffickers have organized a number of clandestine laboratories, scattered as widely as possible and installed on normal traffic routes. These laboratories are installed in countries where it is impossible to exercise a control over products used for concentrating and purifying the drug.

Thanks to the efforts of the police in France and to their co-operation with foreign police forces, it has been possible to deal severe blows to the traffickers. Nevertheless, there are undoubtedly some clandestine laboratories operating in neighbouring countries; in addition, we are convinced that there are other clandestine laboratories in France but that the traffickers, put on their guard by the recent successes of the police and financed by international gangs, have increased their precautions and are exercising great prudence.

Before closing, we should like to draw one more conclusion:

We have seen that (1) a laboratory legally authorized to manufacture morphine or codeine can very well, in the absence of efficient controls, manufacture heroin and sell it on the illicit market for years on end, and that (2) the clandestine manufacture of heroin from opium or crude morphine is, in practice, child's play. These two cases can exist equally well in a country which authorizes the legitimate use of heroin for medical treatment and in a country which prohibits the therapeutic use of heroin, as can be seen from the study in the United Nations *Bulletin on Narcotics* (No. 2, April-June 1953, page 45), which gives a list of cases of clandestine manufacture of heroin discovered since 1945 in various countries.

The facts related above thus show the ineffectiveness of the measures prohibiting the therapeutic use of heroin which were recommended by the General Assembly of the World Health Organization in May 1953.

Fighting the Illicit Traffickers

By George H. White

District Supervisor of the Bureau of Narcotics for the six New England states

Mr. G. H. White has been a federal narcotics law enforcement officer for more than twenty years. He has made narcotics investigations in every state of the Union as well as in Mexico, Canada, India, Iran, Irak, Turkey, the Middle East, France, Italy, Ecuador, Peru and Cuba. He served during the war in the Office of Strategic Services (OSS) in India and the Middle East, with the rank of lieutenant colonel. He is the recipient of the Treasury Department's highest order, the Gold Medal for Exceptional Services.

I was grappling with a small man of 65 years and had managed to lock one bracelet of a handcuff around his wrist. Although ordinarily more than a match for the 150-pound Señor Manuel Jarrín, the Quito altitude of almost two miles had robbed my 210-pound bulk of oxygen and energy and my captive smuggler was fighting for his life and liberty.

My sole ally, much the same size as our quarry, was posing as "Pedro", my chauffeur. Actually, he was Philip Abdón Guerra, colonel of the Ecuadorian Army and chief of all the nation's police.

We were in the process of arresting approximately a dozen Ecuadorians against whom evidence of narcotic smuggling had been secretly gathered over a period of six weeks by a joint effort of the authorities of Ecuador and the United States. I had posed as a buyer of narcotics in large quantities and Sr. Jarrín had considered me a valued customer until I had visited him in his apartment this particular morning with my chauffeur. I made a purchase of three additional pounds of raw opium, whereupon Pedro identified himself as chief of the Guardia Civil and placed Jarrín under arrest.

Sr. Jarrín, apparently incredulous that two such characters — an American dope-peddler and his inoffensive chauffeur — could actually represent the police, violently resisted. In the mêlée, Jarrín was joined by his household of women: wife, relatives, servants. I devoted myself to the prisoner (without too much success), while Colonel Guerra attempted to fend off the enraged attacking Amazons. Although we were both armed with revolvers it was obviously not the time or place to use such weapons. With a black-jack, a short vicious club, I tried to rap the female hands seeking to rescue my prisoner. Suddenly a servant appeared — an Indian woman carrying an infant on her back. In her hand she held a heavy iron skillet. I tried to parry her thrust and failed. The skillet hit me over the left eye. A lucky swing with the black-jack caused the servant to drop the skillet and retreat.

A sudden pounding at the front door announced the arrival of reinforcements. Uniformed officers of Colonel Guerra's command swarmed into the apartment and the fight was over.

The raids, which were conducted in extreme secrecy for almost forty-eight hours, netted a dozen prisoners and huge quantities of narcotic drugs, including heroin, raw opium, morphine, cocaine and marihuana. We also seized a clandestine laboratory and two chemists who had been processing opium into morphine.

This operation, in the spring of this year, resulted from the collaboration between the United States Commissioner of Narcotics, Harry J. Anslinger, and Dr. Camillo Ponce, Prime Minister of Ecuador. Opium poppies were discovered to be cultivated in vast plantations in inaccessible, mountainous regions of Ecuador and the opium was finding its way into the United States and into South American countries. Both Ecuador and the United States were seriously concerned with this novel situation and I was dispatched by Commissioner Anslinger to give such assistance as possible to the Ecuadorian officials. With the assistance of American Ambassador Paul C. Daniels, arrangements were made with Dr. Ponce to permit me to work in an undercover capacity in direct co-operation with Col. Guerra. I was also assisted by a Sr. López, an Ecuadorian who had lived in the United States for many years, who acted as my interpreter.

The most important result of this operation was not the imprisonment of the traffickers for the maximum term under Ecuadorian law, but the public attention brought to a situation which was potentially a great danger to all of the American countries. The opium traffic in Ecuador had grown swiftly and silently. As a result of the investigation, more stringent laws were put into effect by the Ecuadorian Government and greater attention was directed to narcotics law enforcement.

Leaving Ecuador, I proceeded to Lima. Prior to 1948 illicit cocaine was readily available to all comers in the cabarets, bars and hotels. Now, in 1953, I found it was just as difficult to purchase cocaine there, in large or small quantities, as it would be in New York City, despite the fact that

most of the world's supply of cocaine is produced in Peru. This sharp and dramatic change in the clandestine narcotics traffic was brought about by a similar collaboration between Peruvian and United States authorities in 1948. As a result of joint investigations, the cocaine traffic was practically eliminated overnight. Peru enacted laws providing severe penalties for narcotic traffickers and established a squad of the national police to concentrate upon such criminal traffic.

This type of international police co-operation has been particularly effective since 1948. In that year, I was dispatched by Commissioner Anslinger to various Mediterranean areas which were indicated as sources of supply for drugs reaching the United States. I first went to Istanbul and disclosed my mission to high police authorities. They offered and gave ample co-operation. Posing as a buyer of illicit narcotics, I quickly made contact with a ring of smugglers through the proprietor of a low café frequented by seamen of all nationalities. This man, speaking to me through an interpreter which he supplied, arranged for me to meet other members of his organization and in the space of a few days I was prepared to take delivery of a large quantity of heroin which I was presumably to smuggle into the United States. After making final arrangements with the police, I was led to a small house on the banks of the Bosphorus where the drugs were produced and we haggled over the price. The Turkish police had the area surrounded. Detectives disguised as postmen, street-workers, sailors, cab drivers, etc., filled the block, pursuing the occupation indicated by their costume. One crew of detectives, disguised as labourers, even began digging up the cobble-stone street in front of the house. When an agreement had been reached as to price I handed one of the three smugglers present a large sum of money, as it was necessary under Turkish law actually to complete the financial transaction before the crime was technically consummated. I thereupon broke the window of the rear room, the prearranged signal for the police to enter and make the arrests.

Three traffickers and their stock in trade

We had misjudged the amount of noise the breaking of the window would cause and the police did not receive the signal. I had coincidentally identified myself as an American policeman and when the smugglers recovered from their shocked surprise there were indications I was in for trouble. The chief of police had provided me with a small revolver and when the weapon was displayed it caused a temporary lull in hostilities. I thereupon picked up a small wooden chair and hurled it through the window, breaking the remaining glass. Luckily, it hit upon a tin roof on the slope of the hill and this time the police received the signal; sailors, postmen, cab drivers, labourers, etc., suddenly dropped their tools and, to the amazement of spectators, ran to the house, forced the door and entered, capturing all of the traffickers.

Investigation continued and the police located a large clandestine laboratory operated by the gang and seized a total of 18 kg of pure heroin; they also learnt, through interrogation of those arrested, the identity of the other members of this international ring, including persons in the United States.

Two years later I was instrumental in bringing about the arrest of persons in New Jersey, Mexico City, Los Angeles, New York and Florida, on the basis of the clues found on the persons arrested in Turkey.

From Istanbul I went on to Marseilles and, after checking in with the Sûreté, again resumed my role as American buyer of drugs in an Indo-Chinese café of the Old Quarter; I became friendly with a Chinese bartender who spoke some English. I soon

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acquainted him with my purpose and he, in turn, introduced me to the proprietress, a French woman known as "Zizi", a drug addict; she was married to an Indo-Chinese, also a drug addict. I negotiated for the purchase of a large quantity of opium and this was eventually supplied to me in another small café by the French woman, her husband and three Chinese. Inspector Pasquier, of the Sûreté, and the American vice-consul, William Canup, who was acting as my interpreter, had kept me under surveillance, and when the drugs were delivered Inspector Pasquier observed my signal and made the arrests. Pasquier, Canup and I continued the investigation and later in the day Zizi offered to betray her source of supply in exchange for clemency. Her offer was accepted and she thereupon took me to a café in the Corsican section of the city and introduced me to a man known as "Dominique".

I had unwittingly met the principal object of my inquiry in this area. Some months before, a large shipment of heroin had been seized in New York and the seaman smugglers identified their source of supply as Dominique of Marseilles.

We were fearful the news of the arrest of the French woman and her companions would soon become known and it was necessary that we conclude some transaction with Dominique that very night if possible. I explained as best I could, as Zizi interpreted with sparse English, that I was leaving for the United States the following day and required to purchase as large a quantity of heroin as possible before my departure. Dominique replied that it was a little late to visit his plant but that he would obtain as much as he could at the agreed price; he said he would meet me at the usual place.

We departed and rejoined Inspector Pasquier and Vice-Consul Canup. The "usual place", our female collaborator said, was a deserted alley in the Old Quarter, not far from her restaurant, the Manoir. I was to accompany her at the appointed hour into the middle of the alley. Inspector Pasquier and Vice-Consul Canup were to wait at the end, about half a block away. Inspector Pasquier provided me with a pistol and I was to signal the completion of the transaction by firing a shot into the air. Mr. Canup was unarmed and I loaned him the small but efficient black-jack I usually carried. At about eleven o'clock in the evening, Zizi and I approached the rendezvous. It was pitch black and we could see nothing. As we approached the appointed spot, we heard the voice of Dominique who was standing against the wall and invisible until we were within a few feet. I inquired whether he had the drugs and he said he did; he asked whether I had the money and I said "yes". He thereupon opened his shirt and removed a large cloth band with pouches filled with heroin.

At that moment I announced that I was an American policeman working with the Sûreté and fired one shot into the air as a signal. I then grabbed Dominique to prevent his already attempted escape and he struggled vigorously but with little success in view of my obvious physical superiority in years and weight. Suddenly a new factor appeared; Dominique, not trusting his new customer entirely had brought a bodyguard and I was suddenly beset by another man whose strength met the necessary qualifications for his post. During the brief period in which I was alone with this man (the French woman had disappeared) it was clear that I would likely lose both my prisoners and the heroin evidence.

Inspector Pasquier and Mr. Canup were on the job, however, and Pasquier immediately took charge of the unknown bodyguard and secured him by a strangling armlock around the neck. This prisoner, later identified as a young Corsican seaman, continued to struggle violently, whereas I was able quickly to subdue the now unassisted Dominique. Vice-Consul Canup, in his effort to aid Inspector Pasquier in his struggle, swung at the prisoner with the black-jack. Instead of reaching its mark (presumably the Corsican's head) the weapon landed on Pasquier's wrist, breaking it. By this time, the noise of the shot and the general commotion had attracted the uniformed gendarmes who arrived in force, quickly ending all resistance.

After the speedy trial and convictions of the persons involved, I went to Rome. After checking in with the Embassy, I was accredited to the Italian police and I was directed to collaborate with a high police official, Dr. Giuseppe Dosi. He was also the Italian representative on the ICPC, better known as the "Interpol".[1] I again resumed my role as a potential buyer of illicit drugs and quickly secured a contact via a hostess in a basement cabaret, alleged to be owned by the notorious American deportee Lucky Luciano. The proprietor of the Café Liguri arranged for me to meet one of his confederates at my hotel the following morning. When this man arrived, and he seemed vaguely familiar, it appeared from his demeanour that he also had a feeling he had met me before.

He was another of that large colony of deportees from the United States, residing in Rome, most of whom had been deported from the United States for narcotics law violations. As we sparred with each other over a period of several days and many drinks, he finally confessed that he had been reluctant to do business with me because he thought he had recognized me as an American law enforcement official. To my surprise he went on to relate that he thought he knew me, not as a narcotics agent, but as an Assistant United States Attorney who had prosecuted him in New York. It was true that this prosecuting attorney had a very strong resemblance to me and both of us have frequently been asked if we were brothers, which we are not.

This point apparently having been cleared up in the mind of my friend, one Nick di Marzo, he then related that the drug traffic was controlled by the Luciano organization, of which he was a minor member; that the source of supply was at Naples

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[1] International Criminal Police Commission. See *Bulletin on Narcotics*, vol. III, No. 3.

and that he would have to go there to make the necessary arrangements for the quantity of drugs I desired. Negotiations continued over a period of a week and no drugs were forthcoming.

One morning I received a visit at my hotel from the proprietor of the cabaret, Ralph Liguri, also a deportee. Liguri addressed me by my correct name and said he knew all about me. To this day I do not know where he obtained this information. He then defended the reputation of himself and Luciano, saying they were both legitimate business men having nothing whatsoever to do with the narcotics traffic (Liguri had been sentenced with Luciano in the United States for compulsory prostitution and had been deported coincidentally with him). Liguri also displayed an automatic pistol, together with a permit from the Italian police, and warned it would be dangerous for anyone to "frame" him or his associates. I promptly communicated the information concerning Liguri's pistol permit to the Italian authorities who, with equal promptness, cancelled this permit.

It appeared that since I was now well known to the Italian underworld my chance of success here was negligible. However, within a few days, I became acquainted with an entirely different group of traffickers operating between Rome and Trieste. After a week of negotiations under the close surveillance of the police, I arranged for the delivery of a large quantity of narcotic drugs in an outdoor hillside café, some distance from Rome. The delivery was made by four of the conspirators and upon receiving my signal the Italian police closed in and made the arrest without incident. It was not until several weeks later that I learnt one of the criminals caught in the net was Marcello Heinzinger, alias Enzi, who had been listed as an international trafficker in the published U.S. Government black list since December 1934. He had received his first sentence for trafficking in Trieste in 1910. Again, as in the case of Dominique, the netting in of the "big fish" was a lucky coincidence.

As United States narcotics agent, I have made investigations similar to those described in Iran, Irak, India, Palestine, Syria, Lebanon and Mexico. Not all of the journeys resulted in such dramatic episodes as those I have described, but, in each, considerable information of value was obtained, not only for the benefit of the U.S. Bureau of Narcotics, but also for the benefit of the United Nations and the various governments involved.

In every instance, I have found friendly help and whole-hearted co-operation from the authorities of the country in which I was working. I am certain that if other countries found it expedient to send their police agents here, under similar circumstances, we would receive them with equal friendliness.

Because of the peculiar international nature of narcotics law enforcement, complete international co-operation is required, not only on a high policy-making level, but also on a police working level. Since my mission in 1948, numerous other American narcotics agents have travelled throughout the world on similar assignments and have successfully exposed international drug traffickers in their countries of origin. All of us engaged in this work have found the police authorities very pleased to accept our assistance and co-operation in providing detection facilities not always available to them.

Death from Therapeutic Doses of Morphine or Morphine-Scopolamine in Persons Affected by Alcohol or Barbituric Acid

By Knud O. Møller

Dr. Knud O. Møller is Professor at the Institute of Pharmacology, University of Copenhagen. The editors of the Bulletin *felt that, owing to the interest of the subject matter and the high reputation enjoyed by the author, the following article, already published in Danish in* Ugeskrift for Leager *(see bibliography at the end of this issue) should be brought to its readers.*

Few medical practitioners realize that injection of therapeutic doses of morphine or morphine-scopolamine may be directly dangerous to life or fatal to persons seriously affected by alcohol or under the influence of moderate but toxic quantities of barbituric acid. I have found no mention of this in the literature.

My attention was first drawn to the problem by a fatal case which came to us for pharmaco-legal investigation at the Pharmacological Institute (see case 1, the first case here reported). Ascertainment of the cause of death from the results of chemical analysis of the organs, blood, urine, etc., may, through the nature of most of the cases, call for some degree of judgment. The correctness of the judgment will depend principally on the experience of the investigator derived from a long series of similar cases. Since the assessment of such cases may often have serious consequences for the persons concerned — e.g., for a physician who has given a patient a morphine injection — wide experience may be necessary to enable a worker to say with sufficient certainty whether, for example, an injection given by a physician has been the act which led to the death. Our volume of experience in the Medico-Legal Division of the Pharmacological Institute has only recently become large enough to enable us to state an opinion with the necessary certainty. In this paper an account will be given of the most typical cases of death from this cause that we have had to investigate. Space will not permit more than a brief summary of the reports, results of investigation and the like in each case. On the other hand, it has seemed to me necessary to make the case reports full enough to afford documentary support for the conclusions set forth below, so that the reader may to some extent be able to form his own judgment on these.

I should like to emphasize at the start that in most of the cases no blame was attached to the physician who gave the fatal injection, for — as I have already said — the literature has hitherto contained no information about the risk of administering morphine, etc., to persons affected by alcohol or barbituric acid.

Methods, material, etc.

Except for one (case 5), all the cases were sent by the police to our Institute for pharmaco-legal examination, and the information given is derived from police reports, judicial autopsy reports, and the like.

Where any of the present case reports does not mention whether an injection was given intravenously, or by some other route, the reason is that no information was forthcoming.

A judicial autopsy was performed in all the cases, and often a histological examination as well, but the results are not given unless the autopsy or other examinations produced findings different from those usual in persons who have died of narcotic poisoning. The fact that an autopsy and other examinations were performed makes it most unlikely that in any of the reported cases the cause of death could have been other than the poisoning disclosed by the chemical analysis.

All the *analyses* were performed in the Medico-Legal Division (under Fanny Halstrøm, Ph.D., forensic pharmacologist) of the Pharmacological Institute.

Barbiturates are determined by extraction from organs, isolation by sublimation, weighing, and identification by ascertainment of their micro melting-point (Halstrøm, 1940), and sometimes by more special methods (Huang and Jereslev, 1951, and others). The method is quite specific and works with a very small loss. Only unaltered barbiturates are determined.

Alcohol is determined by a special variant of Zeisel's method, which gives very accurate values for alcohol concentration, even in much-decomposed cadaver blood, for which Widmark's method is well known to be useless. The method is controlled by the specific alcohol-dehydrogenization method (Bonnichsen and Theorell, 1950).

From the alcohol concentrations found in the cadaver blood was calculated the approximate alcohol concentration in the blood at the time of injection of the morphine or other substance. The alcohol concentration in the blood of man sinks at an average rate of about 0.15 parts per thousand per hour (between limits of 0.1 and 0.2 per thousand). In this paper, in calculating the earlier blood alcohol concentration we have in all cases *allowed for a reduction in concentration of only 0.1 per thousand per hour*, as alcohol combustion may be somewhat reduced in deeply unconscious persons.

Morphine is demonstrated by chemical and by biological methods (the mouse-tail reaction). *Tropic alkaloids* are demonstrated by a biological method (measurement of pupil diameter in a mouse; Tönnesen, 1948). *Bromide* is determined by the method of Behr, Palmer and Clarke (1930), which gives very accurate results.

The substances referred to in this paper are named as shown below. The list also shows the most important synonyms. "NFN" in the list means the name recognized by the Scandinavian Pharmacopoeia (NFN names). "INN" means International Non-proprietary Names, i.e., the names established by the International Sub-Committee on Nomenclature of WHO. (R) signifies a registered trademark. Morphine in this paper means the hydrochloride and scopolamine the hydrobromide of those substances.

Names used	*Synonyms*
Allypropymal (NFN)	Aprobarbital (INN) = Isonal (R)
Diemal (NFN)	Barbital (INN) = Veronal (R)
Fenemal (NFN)	Phenobarbital (INN) = Luminal (R)
Hexemal (NFN)	Cyclobarbital (INN) = Phanodorm (R) = Cyclodorm (R)
Hypnofen (NFN)	Somnifen (R)
Oxykon (NFN)	Oxykodon (INN) = Eukodal (R)
Pethidine	Pethidin (INN) = Dolantin (R) = Demerol (R)
Tetrapon (NFN)	Approximately = Pantopon (R)

For the sake of comparability, dosage of morphine and scopolamine is given in terms of kilogrammes of body weight. The following note may be of service in evaluating these figures. The usual therapeutic dose of morphine hydrochloride for an adult is 10-30 mg; if the weight is 70 kg, this corresponds to 0.14-0.43 mg per kg; thus the *therapeutic dose of morphine hydrochloride is about 0.15 — 0.4 mg/kg.* The ordinary dose of scopolamine hydrobromide for an adult is 0.5 mg; the therapeutic dose of *scopolamine hydrobromide*, calculated in the same way, is *about 7 µg/kg.*

THE 1945 CASE: DEATH FROM POISONING BY A COMBINATION OF ALCOHOL, MORPHINE, SCOPOLAMINE AND BARBITURIC ACID

Case 1 (Ser. No. 875/1945). A., a wholesale dealer of 48, weight 86 kg.

A. lost his wife a few days before his death on 9 April. On that day his wife's body was taken to the chapel, and in the evening he had dinner with some friends and drank a large quantity of spirits. He was very excited, and his friends, thinking he needed a good sleep, called in a doctor for that purpose.

At 11.30 p.m. the doctor gave a slow intravenous injection of 0.25 g of diemal plus 0.25 g of allypropymal (in the form of hypnofen) plus 15-20 mg of morphine hydrochloride plus 0.4 mg of scopolamine hydrobromide, all mixed together in the syringe. The deceased immediately fell into a deep sleep.

About 1.30 a.m. one of the guests, who had been a nurse, looked at him. He was then dying, and he died immediately afterwards, about two hours after the injection.

Chemical investigation. Barbiturates: Liver, 1.9 mg per cent, muscles, 1.0 mg per cent, urine, 12.3 mg per cent. The diemal was found mixed with another barbiturate. *Alcohol:* Blood, 1.59 per thousand, urine, 2.00 per thousand. *Morphine* demonstrated in the urine; no other poisonous substance could be detected.

Comment

The alcohol concentration in the deceased's blood at the time of the injection was presumably about 1,8 per thousand, a high concentration which probably produced a very powerful effect. The concentration of barbituric acid found in the organs can, according to our experience, be explained only by the injected barbiturate preparation, and by itself would not produce poisoning, let alone death.

An *intravenous* injection of 15-20 mg (= 0.17 - 0.25 mg/kg) of morphine plus 0.4 mg (= 4.7 µg/kg) of scopolamine in addition to the quantities of barbiturate given (0.5 g) into this intoxicated patient at once produced deep sleep, and death occurred two hours later. According to our present experience there can be no doubt that the injection given by the doctor caused the death. The aggregate dose of narcotic substances injected was very large, but not larger than that occasionally used in treatment; and in a person *not* affected by alcohol the injection would probably only have caused a deep and lengthy sleep without harmful after-effects. Even considering that the doctor did not know of the danger of injecting narcotics into a person affected by alcohol, it must nevertheless *be regarded as very imprudent to inject that large a dose of narcotics directly into the bloodstream.* The same facts appear in many of the subsequent cases of poisoning, and the assertion of the danger of intravenous injection therefore applies also to those cases.

MORPHINE AND ALCOHOL

The following cases occurred in persons affected by alcohol who were injected with morphine.

Case 2 (Ser. No. 1099/1947). B., a male factory worker of 48, weight 95 kg.

The history showed that on 25 May, B. drank with his lunch seven to ten glasses of Pilsner and one of brandy. In the evening he had an attack of renal

colic, and at 7 p.m. he took two tablets of some unspecified hypnotic. The doctor who was summoned injected at 10 p.m., to treat the pain, 40 mg of morphine hydrochloride *intravenously*, after which B. fell asleep and snored loudly. Next morning (26 May) he could not be aroused, and was therefore admitted to hospital at 10 a.m. There the typical symptoms of morphine poisoning were found: pupils fully contracted and insensitive to light, marked cyanosis, and deep unconsciousness. He died at 4.50 p.m., almost nineteen hours after the injection.

Autopsy showed that a renal calculus had been recently passed.

Chemical investigation. Alcohol: blood, 0.23 per thousand. *Morphine* detected in liver and muscles. Barbiturates, bromine or other poisons could not be shown.

Comment

At the time of the morphine injection B. must have had at least 2.2 per thousand of alcohol in his blood. The failure to demonstrate barbiturates or bromide means that the hypnotics could not have contributed to the death. The dose of morphine given was very heavy, but the patient's weight (95 kg) must be allowed for; it was 0.42 mg/kg. When admitted to hospital twelve hours after the injection he showed the typical symptom picture of morphine poisoning: marked miosis with cyanosis, which is seen rarely if at all in any other condition. The dose of morphine given (0.42 mg/kg), though very large, will not cause the death of a person who is healthy except for renal colic. The conclusion is therefore that without any doubt the doctor's injection of morphine into a patient affected by alcohol was the direct cause of death.

Case 3 (Ser. No. 1105/1947). C., an inspector aged 39, married, weight 87 kg.

On 6 June between 6 and 12 p.m. he had seven to nine drinks, and some more between midnight and 4 a.m. on 7 June. At about 5 a.m. he suffered from severe pains "in the heart". The doctor who was called in judged that the pain was due to an attack of gallstone colic, and injected at about 6 a.m. 20 mg of morphine hydrochloride intramuscularly and then 10 mg more *intravenously*. C. promptly fell asleep. At 2.15 p.m. the other persons in the house noticed that he was snoring loudly and could not be awakened. He was admitted to hospital at 4.15 p.m. showing the typical symptoms of acute morphine poisoning described above. At 9.05 p.m. he ***died, 15 hours after the morphine injection.***

The *autopsy* showed gallstones, confirming the doctor's diagnosis.

Chemical investigation. Alcohol: blood, 0.68 per thousand. Barbiturates, bromine or other poisons could not be detected; no morphine could be detected in the organs; no urine was found in the body.

Comment

At the time of the morphine injection C. had presumably at least 2.2 parts per thousand of alcohol in his blood. The available methods of morphine determination are relatively so coarse that it is often impossible to show morphine in the *organs* if death occurs a long time after a therapeutic dose; but morphine can usually be found in the urine. The result of the chemical analysis does not therefore conflict with the doctor's report. The dose of morphine given, 0.35 mg/kg (30 mg in all) is within the therapeutic limits. Ten hours after the injection the typical symptoms of severe morphine poisoning were demonstrated in hospital. No other cause of death was shown, and there cannot be any doubt that the morphine injection was the direct cause of death.

Case 4. (Ser. No. 1345/1949). D., a woman of 35, married to a master baker, weight 65 kg.

D. was a troublesome patient, badly in need of treatment, a heavy drinker. She was in hospital a short time — about six months — before her death, with a diagnosis of abdominal colic, and was under observation for ulcer of the stomach, gallstones and misuse of pethidine, in other words, for some very indefinite complaints and for drug addiction. In the afternoon of 12 November she bought three half-bottles of brandy, and after her death one was found empty. The records do not show when she emptied it (see under Comment).

At about 6 p.m. on the same day she called to see a doctor. He was out, and she succeeded after a great deal of persuasion in inducing the doctor's wife at 6.15 p.m. to give her an injection of about 20 mg of morphine hydrochloride (presumably subcutaneous). The doctor's wife explained that D., when she came at 6 p.m., was swaying and had very flushed cheeks and bright eyes but did not smell of spirits.

At 8 p.m. D.'s husband found her unconscious; the doctor, who had by now returned home, was summoned and found her at about 9 p.m. dying, very cyanosed, with Cheyne-Stokes respiration and dilated pupils. She was dead on arrival at the hospital; ***i.e., death occurred about 3 hours after the morphine injection.***

Autopsy showed small stones in the gall bladder.

Chemical analysis. Alcohol: blood, 2.20 per thousand; urine, 2.70 per thousand; stomach contents, 2.90 per thousand. *Morphine* was found in the liver and urine but not in the stomach contents. No barbiturates, bromine or other poison.

Comment

At the moment of the morphine injection D. presumably had about 2.5 parts per thousand of alcohol, perhaps slightly more, in her blood. The time when she took the alcohol is not stated. The description of her condition at 6 p.m. ("swaying, cheeks flushed") may signify that she had taken drink before 6 p.m. On the other side is the note that she did not smell of drink. The fact that the alcohol concentration in the stomach contents was only slightly higher than the probable concentration in the blood plasma (2.2 per thousand in whole blood corresponds to about 2.75 per thousand in the

plasma), and that the concentration in the urine (2.7 per thousand) corresponds closely to the calculated plasma concentration, makes it most unlikely that alcohol was taken after 6.30 p.m. (she was observed between 6 and 6.30 p.m.). The overwhelming probability is that she was under the influence of alcohol when she received the injection but that, being used to drink, she could pull herself together when she was with the doctor's wife at 6 p.m. The doctor's wife left her alone for one minute in the consulting-room, where a bottle of tetrapon was standing in an open cupboard. The fact that no morphine was found in the stomach contents shows conclusively that D. did not take a drink from the bottle of tetrapon. The dose of morphine injected (0.31 mg/kg) is an ordinary therapeutic dose. There can, however, be no doubt that this dose caused the death of the very intoxicated patient. The question whether the alcohol was taken before or after the injection makes no difference to the toxicological conclusions, though it may have a legal bearing.

The wide dilation of D.'s pupils agrees with the general experience that the pupils are dilated before the terminal stage of morphine poisoning.

Case 5 (Ser. No. 36/1939). E., a man of 54, an inmate of a charitable institution.

E. was brought to the police station on 23 December 1938 at 8.30 p.m. for brawling. In the cells he became very violent. Some time after 9 p.m. the doctor who was summoned gave an *intravenous* injection of 10 mg of okykon. A few minutes later E. collapsed, with slowed respiration, deep cyanosis and irregular pulse; he died at 9.50 p.m., about half an hour after the injection.

The *autopsy* revealed marked stasis in all organs but no cause of death.

Chemical analysis (at the University Medico-Legal Institute) showed 2.54 parts of *alcohol* per thousand in the serum and 2.89 in the urine. No special pharmaco-legal analysis was performed.

Comment

At the time of the injection E. presumably had about 2.6 parts of alcohol per thousand in his blood. He was a drinker and apparently a dissolute sort of person. His poor general condition may have contributed to his death. He lost consciousness almost immediately after the injection; this fact, although the dose was relatively small, makes it probable that the *intravenous* injection was the direct cause of death in this highly-intoxicated person. That is all that can be said with certainty about this case.

Morphine-scopolamine and alcohol

It is well known that scopolamine reinforces the depressive effect of morphine on the respiration. Our material also contains cases in which morphine-scopolamine was injected.

Case 6 (Ser. No. 1631/1952). F., male, a manager of 28, weighing 70 kg.

He was an alcoholic. On 10 November at 4 p.m. he returned home from a drinking bout. His wife telephoned to the doctor and said that her husband complained that he could not sleep. At 6 p.m. F. and his wife visited the doctor, who states that *F. was obviously under the influence of alcohol.* F. pestered the doctor to give him an injection to make him sleep; and the doctor yielded and gave him a subcutaneous injection (at about 6 p.m.) of 26 mg of morphine hydrochloride and 0.5 mg of scopolamine hydrobromide.

F. went straight home to bed. His wife went to look at him frequently, and he just lay and snored (nothing else is said about his condition). At 10 p.m. he stopped snoring and died at once, *about 4 hours after the injection.*

Chemical investigation. Alcohol: blood, 1.91 per thousand; in stomach contents, 2.19 per thousand; none in urine. *Tropic alkaloids and morphine* found, but not barbiturates, bromine or other poisons.

Comment

The alcohol concentration in F.'s blood at the time of the injection was probably at least about 2.2 per thousand — i.e., one which is not lethal by itself, especially in an alcoholic. He died about 4 hours after the injection of 0.38 mg/kg of morphine and 7.1 μg/kg of scopolamine, and there can be little doubt that the injection was the direct cause of death.

Case 7 (Ser. No. 1629/1952). G., a farmer of 64, weight 80 kg.

He was an alcoholic, and was sometimes very violent and irresponsible. He had on several occasions assaulted women, and had once attempted rape. On 24 October he rose at 4 a.m., very restless and behaving aimlessly. After lunch he left home, to return about 4.30 p.m. very drunk, irritable and savage. His wife, who was afraid of him, called in a doctor, who, about 6 p.m., injected 20 cg of diemal, 20 cg of allypropymal, 7 mg of morphine hydrochloride and 0.2 mg of scopolamine. He at once became quiet, and it was decided to take him to the mental hospital. In the motor ambulance he lay and snored, dying in it at about 11 p.m., about five hours after the injection.

Autopsy showed that he had moderate sclerosis of the coronary and cerebral arteries and the aorta, but did not show the direct cause of death.

Chemical analysis. Alcohol: blood, 2.23; urine, 3.06 per thousand. *Tropic alkaloids* shown in the urine; *morphine* was not shown for certain. Traces only of barbiturates; bromine or other poisons not shown.

Comment

The alcohol concentration in G.'s blood at the time of the injection was probably at least about 2.7 per cent. He died about five hours after injection of about 0.1 mg/kg of morphine plus 2.5 μg/kg of scopolamine plus 40 cg of barbiturate (2 ml of hypnofen).

The alcohol concentration was very high, and his state of health (moderate coronary sclerosis) was not at all good. The autopsy, even if it could not

demonstrate a direct cause of death, could not disprove that his death was chiefly due to the coronary sclerosis. According to our experience, however, I am much inclined to suppose that the injection of the narcotics was the direct cause of death, and that without it he would have survived his intoxication.

Case 8 (Ser. No. 1634/1952). P., housewife of 33, married, weight 52 kg.

She was addicted to metadon (butalgin). During the previous eight days she had stayed in bed but had nothing the matter with her; her use of medicines during that time was supervised.

On 27 November in the evening she took 15 cg of fenemal, and on 28 November at 6 a.m. she obtained 15 cg of fenemal from the man she lived with, and he then went to work. At 8.45 a.m. he was called home, as she was complaining of severe pains in the back. A doctor was summoned and injected intramuscularly first 1 ml and then, ten to fifteen minutes later, about 0.35 ml of a mixture of tetrapon (for injection) and scopolamine (for injection) in all, that is 8.8 mg of morphine hydrochloride plus 0.68 mg of scopolamine hydrobromide.

Soon afterwards she fell aslep. The man stayed at home. At 3 p.m. she was still breathing, but at about 3.05 p.m. she died.

Autopsy revealed no cause of death.

Chemical analysis: 1.20 per thousand *alcohol* in blood, 1.66 in urine and 1.48 in the stomach contents. Neither barbiturates nor any other narcotic was shown.

Comment

The alcohol concentration in P.'s blood at the time of the injection was probably at least 1.8 per thousand. There is nothing to show when she took the alcohol. She was somewhat underweight, and went to sleep immediately after an intramuscular injection of 0.17 mg/kg of morphine hydrochloride plus 13.1 μg/kg of scopolamine hydrobromide, dying six hours after the injection. The case strikingly resembles some of the previous ones (e.g., 6 and 7).

MORPHINE PLUS SCOPOLAMINE BROMIDE PLUS ALCOHOL

Chronic bromism is probably more wide-spread than is generally supposed. In chronic bromism with clear clinical symptoms, between about 130 and 500 mg per cent of bromine is found in the blood, and life is not endangered until the concentration becomes maximal (400 to 500 mg per cent) (Gundry, 1939; Møller, 1952).

Case 9 (Ser. No. 1180/1948). H., a wholesaler's wife of 48, weight 41 kg.

She was unhappily married and drank, smoked and took hypnotics a great deal. She was always making scenes in the home. In the evening of 9 April she was very restless again. At 11 p.m. she took a little hexomal. She slept a few hours and became restless again, and threw china at her husband. On 10 April at 2.15 a.m. a doctor gave her an intramuscular injection of 15 mg of morphine hydrochloride plus 0.3 mg of scopolamine hydrobromide, after which she was quiet. Her husband saw her at 4 a.m. and at midday; she was lying apparently asleep and was breathing. At 2 p.m. she was found dead and still warm; that is, death occurred about eleven hours after the injection.

Chemical analysis. Bromide: blood, 158 mg per cent; liver, 165 mg per cent, stomach contents 165 mg per cent. Organic compounds of bromine were not demonstrated, at any rate in the stomach contents. *Alcohol:* none in blood but 0.50 per thousand in the urine. *Morphine and tropic alkaloids* were shown in the urine. No other poison was found.

Comment

The urine contained 0.5 parts of alcohol per thousand, showing that the deceased had drunk an appreciable quantity. No alcohol was found in the blood; therefore the alcohol concentration in her blood at the time of the injection could not have been much more than one part per thousand. The urine concentration shows that she must at some time or another have had at least 0.6 per thousand in her blood. Nothing more precise can be said about the alcohol concentration. The blood contained 165 mg per cent of bromide. The ratio between the bromine concentrations in the blood, liver and stomach contents shows that there was an accumulation of bromine in the organism after prolonged use of bromides or of hypnotics containing bromine. Since, moreover, organic bromine compounds could not be shown, particularly in the digestive tract, it is certain that the bromine in the blood came from acute poisoning by a hypnotic containing bromine. The results of the analysis therefore permit the conclusion that H. was suffering from chronic bromism.

She died 11 hours after the injection of 0.37 mg/kg of morphine plus 7.3 μg/kg of scopolamine. The aggregate dose of these substances was not large, absolutely, but was large for a person whose weight was so low (41 kg). In view of these facts there can be little doubt that the injection of morphine and scopolamine caused the death of a person affected by chronic bromism and a moderate dose of alcohol and then by narcotics.

MORPHINE-SCOPOLAMINE AND BARBITURATES

We have had at the Pharmacological Institute during the past fifteen years to investigate an extraordinarily large number of cases of death from barbituric acid poisoning. We have thus gained a very large volume of case material — not yet published — on the connexion between the barbituric-acid concentration in the organs at death and the period elapsing between the time the hypnotic was taken and death. This material enables us to state with a considerable degree of certainty, for the various barbiturates, whether the barbituric-acid concentration found in the organs can be believed to have caused the death within the given period.

Except for one or two cases in which the dose was very large (and the barbituric-acid concentration in the organs correspondingly high) and death occurred in only a few hours, an untreated case of barbituric-acid poisoning will rarely end in death in the first twenty-four hours after the barbiturate is taken. That does not apply to cases in which the patient is exposed to severe chill — e.g., through lying in the open air; but even so the poisoning may occasionally extend over more than twenty-four hours. Nor does it apply where morphine or the like has been injected (or ingested). Some cases of this kind will now be reported.

Case 10 (Ser. No. 1484/1951). K., a workman's wife of 37, weight 45 kg.

K. had "bad nerves" and on this account took a good deal of fenemal. On 9 March at 8 a.m. she was still asleep when her husband left the house. At about 9 a.m. she took, in the presence of her son of 7, a "large number" of *weak* fenemal tablets (15 mg of fenemal each). At 10.30 a.m. her husband returned, summoned by a neighbour, and her usual doctor was called in.

The doctor arrived at 10.45 a.m. She was then *not* unconscious, but very excited. The doctor was shown a bottle which had contained 200 of the tablets (i.e., 3.5 g of fenemal) and was then empty. He had prescribed it for her ten days beforehand. (The number of tablets K. had taken during the previous ten days is not stated.) In spite of this demonstration the doctor injected 11 mg of morphine hydrochloride plus 0.4 mg of scopolamine hydrobromide. K. immediately fell asleep and at 3 p.m. she was found dead. Death therefore occurred six hours after the injection.

Autopsy revealed a few small infarcts in the lungs, but although thrombi were looked for none were found. The cause of death was not shown by the autopsy.

Chemical analysis. A barbiturate, identifiable as *fenemal*, was found: 5.0 mg per cent in the liver and 2.8 mg per cent in the muscles. Morphine could not be demonstrated (a chemical method only was used). The blood and organs contained a small amount of *bromine* (corresponding to about 5 per cent of the total halogens). There was no alcohol.

Comment

The amount of bromine found is quite insignificant (symptoms of chronic bromism do not appear until about 15 to 20 per cent of the total halogens consists of bromine). According to our experience, in cases of fenemal poisoning where death takes place in six hours or less the fenemal concentration found is considerably higher than in this case. It is therefore very improbable that the dose of fenemal taken by K. would have been fatal by itself. The presumption is, therefore, that death was caused by the injection of 0.25 mg/kg of morphine plus 8.9 μg/kg of scopolamine into a person already affected by a narcotic.

The case also shows the excitement which may supervene after the taking of barbiturates and before unconsciousness begins to set in. This was the symptom which induced the doctor to give the fatal injection.

Case 11 (Ser. No. 1252/1949). L., a woodman's wife of 45, weight 62 kg.

On 11 December L. was discharged from hospital, where she had been under observation for gallstones. She was then apparently quite fit. She was said to have been a heavy drinker and in the habit of taking hypnotics to excess.

On 25 December she had a severe attack of pain like those which had gone before. A doctor was called, and at 1 a.m. injected 20 mg of morphine hydrochloride. At 5 p.m. she got up, but at 6 p.m. she had more severe pains and got the doctor to inject 30 mg of morphine hydrochloride. At 9.30 p.m. she went back to bed. On 26 December at 12.45 a.m. her husband noticed that she could not be roused. She was at once taken to hospital, where she was found deeply unconscious with extremely contracted pupils, cyanosis and shallow breathing. She died at 4 a.m., or about ten hours after the last injection.

Autopsy showed no cause of death, and no gallstones or any other explanation of the attacks of pain.

Chemical analysis showed a mixture of *fenemal* and *diemal*: 3.4 mg per cent was found in the liver, 2.3 mg per cent in the muscles, and 5.9 mg per cent in the stomach contents (total 28 mg). *Morphine* was demonstrated in the urine but not in the stomach contents. Neither alcohol nor any other poison was shown.

Comment

The effects of the first injection of morphine (1 a.m.) may be assumed to have substantially worn off, as she had a fresh injection of 30 mg, or 0.48 mg/kg, of morphine at 6 p.m. As in the previous case (case 9), it is very unlikely that the fenemal and diemal she had taken could have caused death by themselves; it must be concluded that the death was due both to the morphine injection and to the barbiturates. In hospital she showed the typical symptoms of morphine poisoning about seven hours after the injection of morphine.

When she took the barbiturates is not known. There is no report that she was showing signs of narcotic poisoning when the doctor gave the injection, and there was therefore nothing to warn him against giving morphine for the severe pains of which she was complaining.

Case 12 (Ser. No. 1363/1950). M., a salesman of 40, weighing 68 kg.

M. had suffered for many years from the after-effects of a chronic encephalitis, and was almost mental and deeply addicted to narcotics. He was a thorn in the side both of his wife and of his doctors. He took a great deal of morphine, as much as 70 mg in twenty-four hours, but during the last few weeks had only had chloral hydrate and some tablets of allypropymal daily.

In the forenoon of 4 January he had *1 g of chloral hydrate.* As he was particularly restless that day and was threatening to kill himself, the doctor injected

at about 2 p.m. *30 mg of morphine hydrochloride*. At 3 p.m. he had *0.30 g of allypropymal* (prescribed by the doctor over the telephone), and at 6 p.m. the doctor injected *20 mg of morphine hydrochloride plus 0.4 mg of scopolamine hydrobromide*. M. at once became quiet. On 5 January at 1 a.m. he was heard snoring. At 6.30 a.m. he was found dead in bed in exactly the same position as when he had fallen asleep after the injection. *Rigor mortis had set in*, meaning that death had presumably occurred not later than 1.30 to 2.30 a.m.

Autopsy. The clinical diagnosis of chronic encephalitis was confirmed by histological examination. No cause of death could be discovered.

Chemical analysis. *Allypropymal*: 1.8 mg per cent in the liver, 1.9 mg per cent in the muscles, 5.7 mg per cent in the stomach contents. *Morphine* was shown in the urine but not in the liver. Alcohol or other poisons were not found.

Comment

The concentration of allypropymal in the organs was a good deal higher than would be expected after an injection of 0.30 g of allypropymal. It is therefore probable that M. afterwards took some, but not much, more allypropymal in addition to what the doctor prescribed at 3 p.m. The presence of allypropymal in the stomach contents bears this out. On the other hand, the concentration of allypropymal in the organs was so low that it is very unlikely that the allypropymal alone could have caused death so soon (presumably seven to eight hours after the last injection). It may therefore be assumed that death was due to the allypropymal in conjunction with the morphine (0.44 mg/kg plus 0.30 mg/kg) and scopolamine (5.9 μg/kg) injected by the doctor. The chloral hydrate can hardly have had any importance.

In addition to the cases just reported, a very short account will be given of *four more cases* in which it is extremely probable that death was due to morphine or to morphine-scopolamine given to patients under the influence of barbiturates.

I. The first case (Ser. No. 1210/1948) was a physically healthy but mentally unsound man who was given an injection of 0.25 mg/kg of morphine plus 6.2 μg/kg of scopolamine plus 20 cg of diemal plus 20 cg of allypropymal by a doctor before being taken to a mental hospital. Shortly before the injection the patient had taken fenemal (which was found in the stomach contents) *without the knowledge of the doctor* and without showing any sign of it at the time of the injection. He died five to six hours after the injection. The rapid death cannot be accounted for by the concentrations of barbiturates shown in the organs, and the injection may be presumed to have contributed to the death.

II. The second case (No. 1199/1948) occurred in a delicate, underweight woman (45 kg), a drug addict, who had been having large *daily intravenous* injections of morphine (150 to 200 mg, or 3.3 to 4.4 mg/kg) and of barbiturates (0.4 g) from her doctor. She became more and more inert and helpless but still complained, and in the last few days could hardly lift an arm. Finally she became completely unconscious and died. It seems highly probable that death was due to the prolonged heavy dosage of morphine and barbiturates. Autopsy did not reveal any cause of death. The result of the chemical examination corresponded to the case history.

III. In this case (Ser. No. 1375/1950) a very restless male mental patient (in hospital) received every day for eight days 0.5 g diemal (*per os*) plus 1.0 g chloral hydrate plus 0.25 mg/kg subcutaneous morphine hydrochloride plus 12.7 μg/kg subcutaneous scopolamine hydrobromide. He died five hours after the last injection. The case is made difficult to assess because the autopsy disclosed an infarct in a lung. No thrombi could be seen with the naked eye but a few appeared under the microscope. This might mean that a circulatory stimulus was present and caused the death. It is, however, fair to stress that there can be no proof that the heavy doses of narcotics led to the death, even if there was a circulatory stimulus. The chronic diemal poisoning which gradually set in (diemal is very cumulative) was reinforced by the injections of morphine-scopolamine.

This case should in my opinion suggest the query whether the "chemical strait-jacket" which has replaced the old mechanical strait-jacket for restless patients may not occasionally present a serious danger.

IV. This case (Ser. No. 1429/1950) is much like the previous one (No. III). A woman mental patient with a strong craving for drugs had been receiving fenemal for a considerable period. During the ten days before she was due to be admitted to the mental hospital she received every day an injection of 0.43 mg/kg of morphine hydrochloride plus 8.3 μg/kg of scopolamine hydrobromide (presumably subcutaneously). After the last injection she at once became very limp and fell asleep, dying about twenty minutes later. The cause of death was not shown at autopsy, and the result of the chemical examination corresponded to the ordinary findings in chronic fenemal poisoning. It may therefore be assumed that death was due to the injections of morphine and scopolamine in a person already suffering from chronic barbiturate poisoning.

In the last case of all the patient received a dosage of narcotics which it would be charitable to call injudicious.

Case 13. (Ser. No. 1272/1949). N., a salesman's wife of 29, weight 78 kg.

N. had fallen from a horse five years before and suffered periodically from severe headaches. During the last month she had not felt well and had stayed in bed. On 14 February she got up.

During her earlier *spells of illness* she had received from her doctor injections of up to 60 to 70 mg of morphine and scopolamine, but not during the last time before 18 February.

On 18 February she fainted and had severe pains at her menstrual period. For the menstrual pains her doctor injected at *8.45 p.m.* 35 mg of morphine

hydrochloride plus 0.1 g of allypropymal plus 0.1 g of diemal (as hypnophen) *intravenously*. As at 10 p.m. the pains had not gone, the doctor injected, again *intravenously*, 15 mg of morphine hydrochloride plus 0.1 g of allypropymal plus 0.1 g of diemal. She then fell asleep. Details of her condition after the injection are lacking. Next morning, 19 December, at 8.30 a.m. a nurse who was summoned thought she could feel a weak pulse, but when very shortly afterwards a doctor arrived N. was dead, about ten and a half hours after the last injection.

The *autopsy* did not show anything in particular.

Chemical analysis. Barbiturates: Liver, 0.7 mg per cent, traces in muscle. *Morphine* was shown in the urine but not in the stomach contents. Alcohol was not found.

Comment

The autopsy did not reveal any morbid changes which could account for the death. The *barbituric acid* concentration in the organs corresponds closely to the information on the amount of barbiturates injected. *Morphine* was found but no alcohol. There was no indication that N. had been able to get at any morphine herself.

During 1¼ hours the doctor injected in all 50 mg, or 0.64 mg/kg, of morphine hydrochloride and 0.4 g of barbiturates, and death occurred about ten hours later. As no other cause of death could be shown, the reasonable explanation of the death is that it was due to the very large intravenous injections of morphine plus barbiturates. Even if N. had been supposed to be a drug addict, she could not be described as a real morphine taker, as she only received it periodically. That menstrual pain should never be an indication for morphine need merely be mentioned.

Discussion

Morphine injected into a healthy adult in doses of 50 to 60 mg will usually produce a deep sleep lasting a variable time, from which the patient can be awakened only with difficulty if at all. To suppress the reflexes — heavy poisoning — often requires a dose, subcutaneous, of about 100 mg (about 1.4 mg/kg). It is usually agreed that the minimum lethal dose of morphine, given subcutaneously, is in the neighbourhood of 100 mg. Death most frequently occurs in ten to twenty-four hours. The toxic and lethal doses of scopolamine are difficult to determine, as the effect of this substance is so variable.

In all the seven *cases of alcoholism* the patient had had a high *concentration of alcohol in the blood* when the morphine, etc., was injected. In one case the concentration may be put at about 1.8 per thousand, and in the others between about 2.2 and 2.7 per thousand. As I said in more detail above, it may be presumed that the injections of morphine, etc., were the direct cause of death in all the six patients and probably in the seventh as well (case 5). This may signify that the morphine, etc., acted synergically with the alcohol.

The literature, as we know, records no investigations concerning *synergism between alcohol and morphine* (though it records some on synergism between alcohol and barbiturates, which will be dealt with in a later paper). Pharmacologically, alcohol is very closely related to *ether* and other narcotics; thus alcohol can produce a deep, reflexless anaesthesia. It is clinically well known that *premedication with 10 to 20 mg of morphine reduces* the amount or concentration of narcotic necessary to induce anaesthesia. I have found only one paper reporting a quantitative investigation carried out in man relating to this question. Turpeinen (1944) determined the ether concentration in the blood of persons in a precisely-defined stage of anaesthesia both with and without premedication, and found in patients who had received 10-12 mg of morphine hydrochloride plus 0.15 mg of atropine sulphate an ether concentration of barely 25 per cent, and in patients who had received 20 mg of morphine hydrochloride plus 0.6 mg of scopolamine hydrobromide one about 50 per cent lower than in patients who had not received any morphine, etc. The author concludes from this that the synergy between morphine and ether is not additive but intensifying (for intensification, see, for example, Møller, pp. 9 and 214).

One would expect at first sight morphine and alcohol to be synergetic. Whether the synergy is intensifying we do not know, though Turpeinen's work suggests that it may be.

The reported cases show that in a certain number of these the injection of 0.3 to 0.4 mg/kg of morphine (cases 2, 3 and 4) caused death in persons with a blood-alcohol content of 2.2 to 2.5 per thousand. Fatal alcoholic poisoning (where no other narcotic is administered) *may occur with an alcohol concentration of 3 to 4 per thousand,*[1] and fatal poisoning may result, as has been stated, from a concentration of about *1.4 mg/kg of morphine.* If the minimum lethal concentration of alcohol is set at 3.5 per thousand, it may be *very roughly* reckoned that in the three cases mentioned (cases 2, 3 and 4) the blood-alcohol concentration reached about 62 to 70 per cent of the minimum lethal alcohol concentration and the injected dose of morphine about 20 to 25 per cent of the minimum lethal dose of morphine. These very rough calculations obviously do not permit a decision whether the synergy between morphine and alcohol is additive or intensifying. The answer may be given by future experiment.

My object in giving these very approximate calculations is to emphasize that pharmacologically it is by no means surprising to observe that therapeutic doses of morphine can cause death in persons heavily affected by alcohol. *The thing to remember first and foremost is that the margin between the alcohol concentration that makes a person thoroughly drunk and that which kills him is very narrow.* (It is well known that the concentration of ether, a close relative of alcohol, needed to produce not particularly deep anaesthesia is about 70 per cent of the concentration which will produce respiratory paralysis.)

[1] We have had such cases in the Institute for investigation.

The fact of *synergy between morphine and barbiturates* is well known both in the practice of anaesthesia and in the laboratory, but we know of no precise investigation of its nature. One case (case 8) shows that *bromides* also can act in synergy with morphine and the like.

The practical therapeutic conclusions of the material here presented should be carefully considered. The injection of morphine, etc., into persons affected by narcotics may be the last straw which breaks the camel's back.

If it is true that ordinary therapeutic doses of morphine or of morphine-scopolamine are dangerous to life and sometimes fatal if given to persons already under the influence of alcohol, barbiturates or bromides, the necessary *conclusion* must be that *morphine and morphine-scopolamine, barbiturates and related substances are contra-indicated for persons under the influence of narcotic poisons.* In other words, before a doctor gives or prescribes these substances he ought always to consider whether in the particular case there is reason to suppose that the patient is already under the influence of narcotics. It will naturally be impossible in every case to be certain that this contra-indication is not present. In the short case report No. I (Ser. No. 1210/1948) the patient had taken fenemal just before the doctor arrived and was showing no sign of it when the injection was given. On the other hand, in case No. 9 the doctor injected morphine-scopolamine although he had been expressly warned that the patient had taken fenemal; and in case No. 6 the patient was obviously intoxicated when the injection was given.

It appears from the case reports that in a relatively large number of cases the fatal morphine or morphine-scopolamine injections were given *intravenously*. There can be no doubt that the danger of poisoning from these substances is considerably greater when they are given intravenously than subcutaneously. The very high temporary concentration in the blood caused by an intravenous injection can have such a strong depressive effect on the respiratory and vasomotor centres that a *vicious circle* is set up which, assisted by the lower but persisting concentration of morphine, etc., in the blood, produces a fatal impairment of the vital functions.

Moreover, euphoria is specially intense after an *intravenous* injection, and an *intravenous* injection of morphine has in many cases led to morphine addiction. For the reasons given, *morphine and related substances should be injected intravenously only in very rare cases, and then only in moderate doses.* I derive the impression from many cases that intravenous morphine is given relatively often in Denmark.

I am well aware that this question will be asked: what is a doctor to do with a patient in a state of strong excitement caused by alcohol or barbiturates? The only answer I can give is that the condition should never be treated with drugs; the only effective ones here are narcotics, and they endanger life and are sometimes fatal.

There remains, besides the problems dealt with here, the other problem of the simultaneous effect of alcohol and barbituric acid. This will be considered in another paper.

Summary

1. An account is given of a series of cases showing that the injection of therapeutic doses of morphine or of morphine-scopolamine into persons already suffering from the effects of alcohol, barbiturates or bromides in non-lethal quantities may cause death, often with the characteristic symptoms of morphine poisoning.

2. Morphine works synergetically with alcohol, barbiturates and bromides.

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The Physical Methods for the Identification of Narcotics

A series of articles, written under the direction of Charles G. Farmilo and Leo Levi

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PREFACE

The study of narcotic properties, analgesia and addiction liability has led scientists to the discovery of new narcotics with more or less addiction liability. The numbers of narcotics have thus increased far beyond the original natural opiates. The need for strict control and wider investigation of potentialities of the increasing numbers of narcotics makes it imperative, therefore, to have up-to-date means of identification for forensic purposes, and for scientific investigation.

In a study of the identification problem over the past five years, it became apparent that along with microchemical data the physical data about narcotics were required for complete identification. It was also apparent that there is a paucity of narcotic physical data. It was decided to orient our efforts toward the collection and co-ordination of both types of data. In contrast to the lack of physical data, a great number and variety of microchemical crystal and colour tests are scattered in the chemical literature. We hope eventually to assemble all the pertinent analytical knowledge in chemistry on the subject of narcotic identification. It is obvious that the achievement of this aim can be brought about only by the collaboration of many authorities. It is hoped that these papers will begin by helping our colleagues in their research and solution of practical identification problems and that they will collaborate with us by helping to keep the material up to date in subsequent issues of the *Bulletin on Narcotics*.

The authors wish to express their appreciation to the many people who have helped in beginning this project. The whole-hearted co-operation of Dr. L. I. Pugsley is appreciated in generally guiding with his extensive technical knowledge the over-all task. Dr. W. Barnes, National Research Council, collected the X-ray diffraction powder photographs and data. Defence Research Chemical Laboratories made a substantial contribution by providing us with the infra-red spectra, obtained under the supervision of Dr. Charles Hubley. Mr. Charles Fulton has contributed his help on various problems.

The various drug companies have been extremely generous in their gifts of valuable and sometimes rare materials. Drs. Reti and Castrillon, of the South American firm, Atanor, contributed the newly discovered trichocereine. Dr. Léo Marion of the National Research Council, Canada, supplied the authentic protopine used in these studies.

To the typists, draughtsmen and photographers of the National Research Council, Canada, and National Health and Welfare we owe thanks for cheerful and optimistic co-operation.

Acknowledgment is also made to the officials of the Department of National Health and Welfare who gave us permission to publish these data.

Following is the general plan for the present series:

IA *Introduction to Identification of Narcotics by Physical Methods* by Charles G. Farmilo and Leo Levi, Organic Chemistry Section, Food and Drug Laboratories, Department of National Health and Welfare, Ottawa

IB *The Common Physical Constants for Identification of Ninety-five Narcotics and Related Compounds* by Charles G. Farmilo, P. M. Oestreicher and Leo Levi, Organic Chemistry Section, Food and Drug Laboratories, Department of National Health and Welfare, Ottawa

IIA *The X-ray Diffraction Method on Powder* by W. H. Barnes, Division of Physics, National Research Council, Ottawa

IIB *X-ray Diffraction Data on Powder for Eighty-three Narcotics* by W. H. Barnes and Helen M. Sheppard, Division of Physics, National Research Council, Ottawa

IIIA *The Ultra-violet Spectrophotometric Method* by Charles G. Farmilo, Food and Drug Laboratories, Ottawa

IIIB *Ultra-violet Spectral Data for Eighty-six Narcotics* by P. M. Oestreicher, Charles G. Farmilo and Leo Levi, Food and Drug Laboratories, Ottawa

IVA *The Infra-red Spectrographic Method* by Charles Hubley and Leo Levi, Defence Research Chemical Laboratories, and Food and Drug Laboratories, Ottawa

IVB *Infra-red Spectra of Narcotics* by Charles Hubley, Leo Levi and Moira Smith, Defence Research Chemical Laboratories, and Food and Drug Laboratories, Ottawa

PART IA

Introduction to Identification of Narcotics by Physical Methods

By Charles G. Farmilo and Leo Levi

Table of Contents

Section		Page
1.	Object and trend in recent research on narcotic identification	21
2.	General problem of narcotic analysis and relation to organic analysis	21
3.	Crystallographic methods	24
4.	Optical crystallography	24
5.	X-ray diffraction	24
6.	Optical rotation	24
7.	Methods based on chemical groups in narcotics	24
	(*a*) Spectrographic methods of determining chemical groups	25
	(*b*) Infra-red and Raman spectra	25
	(*c*) Ultra-violet spectra	25
	(*d*) Luminescence spectra	26
8.	Electromotive force measurements on narcotics	
	(*a*) Electrometric titrations	26
	(*b*) Polarography	27
9.	Conclusions	27

Table

I.	Chemical groups present in narcotics and related compounds detectable by physical methods of identification	28
II.	Phenanthrene type narcotics and related compounds, ultra-violet chromophores and detailed structure	30
References		31

1. Object and Trend in Recent Research on Narcotic Identification

The object and characteristic trend of recent research into methods of narcotic identification for forensic purposes has been that of obtaining definite identifications on minimal quantities of generally impure substances, without destroying or altering the whole sample.

There are two practical reasons for this trend in forensic research. First, seizures of drugs by the police are often small and so heavily adulterated that they contain only small amounts of active components; and second, to facilitate court procedures rapid accurate methods of analysis are required which leave a certain amount of sample for a court exhibit and yield specific identifications. As early as 1880 it was realized (1)[1] that drug identification for court purposes could be considerably aided by instrumental methods (e.g., spectroscopy). It was not until about 1920 that in Europe forensic scientists in universities began to advocate the extended use of physico-chemical methods of identification in medico-legal and toxicological cases (2). This development ran concurrently with the growth of theory and practice of physical chemistry; and about 1940 with the introduction of electronic circuits and recorders, instrumentation developed to the routine stage of usefulness (3). Some delay in general use of instruments is probably caused by the lag in applications of instruments behind theoretical development, and delay in co-ordination of the theory and practice of instrumentation with chemical findings. It is hoped as a general objective of the present series in regard to narcotics to alleviate this situation. It is the object of this paper first to point out the usefulness in narcotic analysis of a number of physical methods and second to introduce a series of papers which describe for narcotic analysts the principles and practice of X-ray powder diffraction, and ultra-violet and infra-red spectroscopy. These papers have been divided into an introductory and an experimental part. In the latter the common physical constants, X-ray powder diffraction photographs, and ultra-violet and infra-red spectra of about ninety-two narcotics and related compounds are collected. This introductory paper to the series tries to point out a general approach to the problem of research on methods of narcotic analysis on the basis of qualitative organic chemical analysis in order to show the importance of a combined study of physical and chemical methods.

[1] Figures in parentheses throughout the text refer to the numbered publications listed at the end of this article.

2. General Problem of Narcotic Analysis and Relation to Organic Analysis

Like other schemes of qualitative organic analysis (4, 5), analysis for narcotics in an unknown sample involves several steps beginning usually with some dividing test which puts the unknown in one or the other of two classes, on the basis of a general property such as the solubility. Also, since most narcotics are amines or their salts, the initial classification is often made by means of general amine precipitants. Assuming the possible presence of a narcotic is indicated, then very small samples are made to undergo physical and chemical changes by means of specific tests, usually microscopic. From results of these chemical tests, inferences are drawn, and on this basis the unknown is restricted to fewer and fewer subdivisions of a particular chemical class. It becomes possible, by combining all the known data, to find a narcotic that shows complete physical and chemical similarity when put through the same tests as the unknown, and therefore is identical with the unknown under investigation.

The narcotic analyst is faced with special problems which force him to evolve certain special steps, or modify existing ones, to enable him to systematically identify the more common narcotics in microquantities; at the same time he has to be prepared to eliminate or identify all drugs which are presented in the course of police investigations. The sample to be analysed for a narcotic may be in one of several forms: such as traces of drug on the addict's paraphernalia, as a spoon, medicine dropper, needle, or swab of tissue paper or cotton; a natural product such as raw opium, coca leaves, *cannabis sativa* or

a mixture of tobacco and marihuana; a capsule, or a "deck" containing a powder; or a liniment, or elixir or other legitimate pharmaceutical preparation containing one or more active ingredients. Samples of narcotics may also be isolated from human tissue obtained after autopsy, or in urine or saliva from "doping" of race horses. In the last two toxicological types of cases, narcotic isolation and purification require procedures especially designed for the purpose (6, 7). In the case of pharmaceutical preparations the sample can often be dissolved in water and shaken out with immiscible solvents from acid or basic solutions. In such a case the mode of separation usually yields enough solubility data to classify the unknown compound to a certain extent. In the case of a narcotic isolated from a pharmaceutical preparation, even a boiling point or melting point may be obtained. Such physical constants are at present rarely determined in routine narcotic identification. The fact that many samples may contain only trace amounts of the drug (which cannot be completely destroyed because of court purposes) often precludes rigorous extraction and purification procedures, or determination of ordinary physical constants which involve recrystallization or distillation, for fear of destroying the whole sample. It is the condition of sample therefore to a great extent that determines the over-all and final procedures adopted in analysis.

In the following summary the steps usually followed in narcotic analysis are outlined in a form similar to the one generally used by textbooks for organic analysis. A number of these steps are explained in order to bring out the similarities and differences between narcotic analysis and classical organic procedures in use since the time of Liebig. The steps for narcotic analysis follow the outline given by Cheronis and Entrikin (5). It will be noted that steps B_1, B_3, B_4, and D are different from ordinary organic identification procedures. They consist of examination to detect the narcotic constituent, type of physical constants, colour and classification tests, and type of derivative formation. Although in laboratories specializing in organic chemistry it is often the routine procedure to determine physical constants prior to beginning actual detection of chemical groups, the nature of narcotic analysis sometimes makes this the last step to be performed. Often a qualitative identification is the only one required by police officers to aid in investigation, or in court procedures. This qualitative identification, at present, is made on the basis of chemical findings.

Summary of steps in narcotic analysis

A. *Isolation and purification:*

1. Separation of the drug from the adulterant.
2. Sublimation, distillation, recrystallization.

B. *Examination and classification of the drug:*

1. Determination of physical constants.
2. Solubility classification (usually indirect information obtained from step A 1).
3. Qualitative analysis by precipitating reagents to determine if an amine type compound is present.
4. Classification by means of precipitation, and colour reactions with certain types of reagents.

C. *Co-ordination of data:*

All data including physical constants must be carefully co-ordinated and compared with the chemical literature and collections of data and other sources. A list of possible compounds prepared and the narcotic that best fits the data is then selected as the probable one.

D. *Derivatization and final proof:*

By means of microchemical crystal reactions suitable derivatives of the narcotics are prepared. Reagents yielding the best crystal tests with the probable narcotics are selected. If the selected derivative has the characteristic form described in the literature for a probable narcotic, the identification is regarded as tentative. Finally, if the forms of other characteristic derivatives prepared from the unknown, and from a pure sample of the narcotic, are identical, the proof is considered conclusive.

Classification of the unknown narcotic by reference to its behaviour towards typical reagents is still the most common method of detection. Many microchemical and colour tests are available for helping to classify narcotics. These have recently been reviewed for the new synthetic narcotics by Farmilo, Levi, Oestreicher, and Ross (7). A great deal more information regarding analysis of narcotics and other toxicologically important drugs is still scattered in the chemical literature and various laboratory files. Attempts to co-ordinate this information are being made in the Alcohol Tax Unit Laboratories of the U.S. Treasury Department, United Nations Narcotics Laboratory, New York State Racing Commission Laboratory, the Attorney General's Laboratory of the Province of Ontario, the Royal Canadian Mounted Police Crime Detection Laboratories at Ottawa and Regina, and Canadian Food and Drug Laboratories of the Department of National Health and Welfare, and by organizations such as the Forensic Society of Canada and the American Academy of Forensic Sciences. Publication of reviews of data, by such groups, will eventually simplify the search for now widely scattered information on narcotics. However, such reviews are just beginning to be made and most of these laboratories have still to rely on their own collections of data and more often on the skill and knowledge of one or two experienced analysts.

In a practical case after co-ordination of data is achieved, during analysis of a sample, there may still be a number of possibilities in addition to the particular narcotic tentatively concluded by the analyst to be present. In the classical organic procedure at this step the analyst prepares one or more suitable crystalline derivatives of the unknown compound based on the tentative identification. In forensic analysis the step of derivative formation is carried out in a special way by means of microchemical

crystal reactions. The analyst identifies the substance by a microchemical reaction based on the appearance, under the microscope, of the derivative as it begins to crystallize on the microscope slide. By reference to the same test, with the known compound as the standard of comparison, and a written description or an illustration such as a line drawing or photomicrograph of the crystal product, the analyst makes his final decision as to the identity of the unknown. He is then able to select a number of additional best crystal tests to confirm his decision.

Experience has shown (8) that when the product of the reaction of narcotic and reagent is distinctive and readily formed, the microscopic method leaves little to be desired. Usually mere inspection with the microscope is satisfactory—when the crystals are truly characteristic (9). Sometimes, however, still further work has to be done by the analyst.

Where truly characteristic microcrystalline forms cannot be obtained in microchemical reactions, further derivitization is required by the analyst to satisfy him as to the complete identity of the unknown. It is often possible for the analyst to isolate the same crystalline derivatives as were obtained in the microcrystal tests for recrystallization and further characterization. A few of these products have already been isolated and purified for further study; for example, reineckates of quite a few amines, amino acids, and quaternary ammonium bases are derivatives having sharp melting points. Levi and Farmilo (10) showed that a number of narcotics from the diarylalkone-, arylpiperidine-, and hydrophenanthreneamine subdivisions of the chemical narcotic classification gave crystalline reineckates. Similar studies of morphine-Marme and morphine-Mayer reactions have been made (11). Cadmium halide complexes of a number of nitrogenous bases including narcotics have been prepared and quantitatively estimated by means of non-aqueous titration of the complexes in glacial acetic acid (12). The foregoing examples serve to illustrate some of a large number of derivatives which can be employed and further investigated for use in identifying narcotics. Many more reagents remain to be studied.

Ordinarily for purposes of organic chemistry in dealing with pure compounds the readily determinable, more common physical properties enable one to exclude from consideration all but a very few of the known compounds. This is not the case in narcotic identification, which has become more complicated as new products are marketed. The recent discovery (13) of the relationship between structural and optical isomers with analgesic and addiction potentialities has resulted in commercial production of diasteroisomers, such as *d*-α-, *l*-α-, *dl*-α-, and *d*-β-, *l*-β-, *dl*-β- methadols and acetylmethadols (14) and *dl*-α- and β- prodines (15). Such diasteroisomers differ from each other only in physical properties such as optical rotation, melting point and solubility. Their chemical reactions are of the same type for all forms since they possess the same functional groups, but their rates of chemical reaction and biochemical activity in man (16) and animal (17) are different. In ordinary organic chemistry a sharp melting point or boiling point, together with qualitative and quantitative analysis for elements, refractive index, optical rotation, and chemical reactivities suffice to identify the organic substance. However, the commonly used physical properties are found by experience to be most often of little use in narcotic analysis. Narcotic samples, especially salts, rarely display sharp and reproducible melting points; decomposition over a temperature range often is observed. The molecular weight and empirical formula cannot be readily determined with sufficient accuracy to remove ambiguity, due to uncertainty of the hydrate forms and high molecular weights. Refractive indices for crystalline narcotics are not as commonly given as they are for liquids. These various factors plus the rapid development of the number of commercially available narcotics make it extremely important to investigate other well established physical methods of organic chemistry for use in narcotic identification.

For this purpose it will be useful to refer back to the summary of steps in narcotic analysis to determine where further information is required.

Review of the steps of identification shows that three types of properties are used in narcotic analysis: physical constants based on colligative properties depending on number of molecules; constitutive properties, depending on the size and shape of the atoms and molecule; and chemical properties governed by the functional or chemical groups in the narcotic. Accordingly the physical methods of organic chemistry which we propose to study in connexion with narcotic identification are shown in the following classification according to the molecular property which each measures:

Classification of physical methods of organic chemistry useful in narcotic identification

A. *Methods based on size, shape and atomic configuration of the molecule*

1. Optical crystallography
2. X-ray crystallography
3. Polarimetry

B. *Methods based on chemical groups present in the molecule; spectrographic methods*

1. Ultra-violet
2. Infra-red
3. Raman
4. Luminesence

C. *Methods based on chemical groups and numbers of molecules*

1. Electromotive force measurements. Electrometric titrations in aqueous and non-aqueous solutions
2. Polarography

All the methods under A and B and C in this classification yield physical constants; these, coordinated with results from chemical tests, lead to complete identifications. By itself a single method, chemical or physical, is not sufficient as a basis for determining identity; for example, in the cases of A3 and B1 a specific rotation or ultra-violet spectrum

alone would not be sufficient. The optical and X-ray crystallographic methods A1 and A2 are the ones most likely to be self-sufficient in a given case. A certain judicious choice of method for completing the identification is therefore necessary. This choice has to be based on a knowledge of the principles and limitations of each of the methods listed.

The physical methods listed in the above classification will be discussed briefly in the following text, with statements of the main principles and limitations of each method, the object being to show how specific methods in two main groups of physical methods overlap in effect and results. Thus a guide to those planning the use of one or other of these methods in organic identification will be provided.

3. Crystallographic methods

A crystallographic description (which ideally includes optical and X-ray crystallography) is a unique set of physical characteristics which, when specified, would completely determine the crystalline phase, with respect to size, shape and atomic configurations. The important directional properties of crystals brought about by virtue of the orderly arrangement of their constituent atoms and molecules provide the basis for such crystallographic descriptions. Unfortunately facilities for complete crystallographic identification are not available to most investigators who isolate new compounds, nor to analysts who are required to detect drugs for law enforcement purposes. Therefore crystallographic descriptions for only a few narcotics are available. The value of crystallography in drug identification is, however, so obvious that a number of laboratories doing forensic work are using these methods to obtain identification data.

4. Optical crystallography

More than thirty years ago Wright (18) and Wherry (19) working in United States Government laboratories applied the immersion method of determining the refractive indices of crystals with the polarizing microscope in chemical analysis. Chamot and Mason (26) developed the technique of chemical microscopy in this connexion. Keenan (20) and others (21) in U.S. Food and Drug laboratories and elsewhere have described the use of optical crystallography for routine identification of alkaloids and synthetic drugs (22, 23, 24 and 25).

Optical data readily obtainable include the refractive indices, and sometimes the interference figure, the optic sign, optical dispersion, pleochroism, and the rotation of the plane of polarization. Textbook descriptions of the techniques are given in references 26, 27 and 28 for those interested in further details on the subject.

5. X-ray diffraction

The constituent atoms of crystals are arranged in regular three-dimensional structures and their centres are separated by distances of the same order of magnitude as the wave-lengths of X-rays. Finely powdered crystalline materials give X-ray spectra that are eminently suitable for identification purposes. In fact an X-ray diffraction photograph obtained on the powdered substance is by itself usually sufficient for unequivocal identification, except in the particular case of distinction between *d*-, and *l* optical isomers. This method of identification together with experimental data for eighty-three narcotics is discussed in parts IIA and IIB of this series (29 and 30).

6. Optical rotation

Optical rotation has long been used as a physical constant in organic characterizations. The organic chemist for about 100 years has defined polarimetry in terms of investigation of the quantitative changes of direction of the plane of vibration of linearly polarized light during its passage through optically anisotropic liquids or solutions. The specific rotation of a substance in solution is calculated by the formula: $[\alpha]\,D^{25\ degrees} = \frac{100a}{lc}$, where $[\alpha]D^{25\ degrees}$ = specific rotation at $25^{degrees}$ C; a = observed rotation; l = length of tube (decimeters); d = density; c = g in 100 cc of solution.

The subject of polarimetry has been reviewed recently by W. Heller (40). The specific rotations for about thirty narcotics will be given in part IB of this series (41).

7. Methods based on chemical groups in narcotics

A chemical classification of narcotics and some related substances is shown below. This divides the substances into four main families and a number of subdivisions in each family, which depend on the main structure. In table I some chemical groups of the molecules of narcotics and related compounds are listed for the purpose of specifying the methods by which they are most likely to be detected. The list shows how physical methods may be applied to the problem of narcotic identification.

CHEMICAL CLASSIFICATION OF NARCOTICS AND RELATED COMPOUNDS FOR IDENTIFICATION

1. Pyrans
   - meconic acid
   - pyrahexyl

2. Aryls

(a) *Arylcarboxylic acids*
- benzoic acid
- opianic acid

(b) *Arylpiperidines*
- cocaine
- ecgonine
- pethidine
- ethylpethidine
- α-prodine
- β-prodine
- hydroxypethidine
- methylketobemidone
- ketobemidone
- propylketobemidone
- acetoxyketobemidone

(c) *Diarylalkoneamines*
- isomethadone
- pipidone
- methadone
- phenadoxone
- α-methadylacetate

(d) *Arylethylamines*
- mescaline
- trichocereine
- narceine
- ethylnarceine

3. Isoquinolines

(a) *Dihydroisoquinolines*
- cotarnine
- hydrastinine

(b) *Phthalideisoquinolines*
- narcotine

(c) *Benzylisoquinolines*
papaverine
dioxyline phosphate
laudanine
cryptopine
protopine

4. PHENANTHRENES

(a) *Phenanthroisoquinolines*
apomorphine
morphothebaine

(b) *Phenanthroethanoamines*
thebenine

(c) *Iminoethanophenanthrenes*
3-hydroxy-N-methylmorphinan
3-methoxy-N-methylmorphinan
sinomenine

(d) *Iminoethanophenanthrofurans*
morphine
codeine
neopine
thebaine
dihydromorphine
dihydrocodeine
dihydromorphinone
dihydrocodeinone
methyldihydromorphinone
dihydrohydroxycodeinone
ethylmorphine
benzylmorphine
α –monoacetylmorphine
diamorphine
acetyldemethylodihydrothebaine
morphine-N-oxide
N-allyl-normorphine
pseudomorphine

(a) *Spectrographic methods of determining chemical groups*

The majority of chemical groups in table I show their effects in particular regions of the spectrum in the ultra-violet, infra-red, and Raman spectra. Since we are limited in this project to compounds in only four major chemical homologous series, it is possible by detecting the absence of a particular group to eliminate by means of a single criterion a number of compounds. The reverse is not generally true; the application of a single criterion does not establish the presence of a chemical group, nor indicate a particular compound. The study of many members of a homologous series is necessary before empirical rules can be established by which the spectral region for a chemical group can be determined. The prediction of frequencies for groups, and identifications therefrom, will become more exact as the methods are further investigated. For present purposes a statement in very general terms of the main principles and applicability to narcotic identification will be given.

(b) *Infra-red and Raman spectra*

In a molecule, the size of the atoms and magnitude of the forces holding these atoms together affect its vibration frequencies. Both Raman and infra-red methods detect these vibration effects. The atomic and molecular vibrations correspond exactly to the frequencies of the infra-red vibration absorbed by the atoms. The infra-red vibration frequencies most useful to the chemist are located in the range from 4,000 to 100 wave numbers, corresponding to 2.5 and 100 microns respectively. The Raman effect is revealed as a line spectrum in the same region as the infra-red; for example, the C-H bond has one Raman frequency between 2,700 and 3,000 wave numbers, the exact frequency being dependent on the chemical environment of the group. Fine distinctions in structure are thus theoretically detectable; for example, the C-H bond in the methane, methyl, methylene, and methylidene groups have different frequencies in this range.

The Raman effect is brought about as follows: in general, a transparent medium illuminated by monochromatic light scatters light at the same wavelength as that of the incident light, and light of modified wave-lengths, the frequency difference between the incident and modified light being related to vibrational and rotational frequencies in the molecule.

The theory of the Raman effect shows that Raman frequencies are closely related to frequencies of vibration within the molecule. A Raman spectrum is a manifestation, therefore, in visible or ultra-violet light, of a molecular process which gives rise to absorption in the infra-red, but it should be noted that for molecules of high symmetry not all infra-red frequencies have Raman counterparts or vice versa. The determination of Raman spectra consists of measuring the frequencies or wave-lengths of the lines, their intensities, and states of polarization (a line produced by unpolarized light may be more or less polarized depending on the symmetry of the molecular vibration). The measurement of polarization state of a line is difficult and requires extra experimental precautions and usually is dispensed with in applications of Raman spectra to analysis (31).

With regard to obtaining Raman spectra of narcotics, it should be noted that solubility of the molecule will be important. In principle, Raman spectra (with one limitation) should be obtainable; however, in practice it is not possible to obtain Raman spectra in water solution unless a solubility of 1:5 in terms of mole fraction is available. This means, in other words, that one molecule of narcotic has to be present for every five of water, and such molar solubilities are not the usual ones encountered with narcotics, which presents a serious limitation for using Raman spectroscopy in routine analysis. It should be noted that organic solvents with higher molecular weights than water may be usable as solvents for narcotic bases, thus reducing the molar ratio of absorbent to solvent to a more favorable fraction, say 1:1. Another possibility does exist, however, and this is with regard to obtaining Raman spectra of solid materials. The experimental difficulties in the handling of solids for obtaining Raman spectra are greater than for solutions and present a practical limitation. Another theoretical limitation may be encountered with certain compounds. Those molecules whose electrons can be excited to certain electronic states from which the electrons return to the ground states at a relatively slow rate will give rise to emission fluorescence spectra, which masks any Raman effect. However, these effects give rise to "decay" or luminescence spectra which may be important since luminescence spectra are in themselves useful for identification. Such spectra will be referred to again.

(c) *Ultra-violet spectra*

Ultra-violet and visible spectra involve changes in electronic energy of the groups in contrast to infra-red and Raman effects. The region of the spectrum with which we are concerned ranges from 50,000 to 100,000 wave numbers. Groups of atoms which have electronic structures which interact with the electromagnetic wave and involve the structure in energy

changes can absorb energy. For example, groups containing multiple bonds which are fundamentally responsible for the colour of organic substances, and are called chromophores, also show absorption of light in the ultra-violet. A number of such chromophores is shown in table II. Numbered formulae of phenanthrene and morphine are shown in table II as a basis of comparison for other phenanthrene-like narcotics listed in column 2 containing the related chromophores.

The use of ultra-violet spectra for narcotic qualitative analysis depends on interpretation of characteristics of the spectra. The characteristic spectral curves cannot yet be explained in simple terms, since no apparent direct relationship appears to link the frequencies in this range with the size or binding force of the atoms (composition of the chromophore) as it does in the case of atomic vibration frequencies. The frequency decreases (wave-length increases) as the size of the conjugated system increases. Also in some cases two chromophores occur in molecules, and are separated by a methylene group and the total absorption is the simple sum of the absorption of the groups as if they were in separate molecules. Such generalizations, although of theoretical value, do not help to identify a narcotic. The value of ultra-violet absorption spectra in analysis rests wholly upon the identity qualitatively and quantitatively of the ultra-violet absorption curve of an unknown narcotic, with that of a known narcotic having a known chromophore or absorbing group.

(d) *Luminescence spectra*

Certain emission spectra are of interest in drug analysis either for the purpose of identification or estimation; these are classed as luminescence spectra (31). Fluorescence, phosphorescence, chemi-and electroluminescence are examples. Fluorescence involves electronic excitation of a molecule by absorption of light, and the principles of intense illumination and of avoiding spurious radiation in the emitted light apply, and in general the typical Raman arrangement is used (32). Fluorescence phenomena have been used in alkaloid analysis since 1885 according to Fisher in his review of physical methods applied to forensic medicine (2). A recent review of fluorimetry by White (33) indicates the extensive application to analysis of organic materials. As far as can be determined no fluorometric procedures for narcotics have been studied. A general description of means of obtaining and use of fluorescence spectra as a tool for organic research was given by Kasha (42).

8. Electromotive force measurements on narcotics

(a) *Electrometric titrations*

Certain acidic and basic groups commonly present in narcotics may ionize in water or other polar solvents and are characterized by dissociation constants. Dissociation constants are a measure of acidity or basicity of narcotics and can be obtained by electrometric titrations. Those groups in narcotic molecules which respond to such measurements are shown in table I in column 3, designated by means of the letter E.

The acidic dissociation constant exponent, pK_A of alkaloids in various solvents is found from the titration values of the pH ⅓, pH ½ and pH ⅔, read on a pH meter where the fractions ⅓, ½ and ⅔ represent degrees of neutralization. The pK_A values are derived from the dissociation constant as follows. By definition

$$K_B = \frac{[QH^+]\ [OH^-]}{[Q]} \quad (1) \text{ and } K_A = \frac{[H^+]\ [Q^-]}{[QH^+]} \quad (2)$$

where the quantities in square brackets are molar concentrations of ion or undissociated molecule, Q referring to undissociated alkaloid, QH^+ to the alkaloid ion, K_A and K_B being the "acid" and "basic" dissociation constants of the latter respectively.

From (2) $\left[pK_A = pH + \log \frac{[QH^+]}{[Q]}\right]$ (3); at ½ neutralization $\frac{[QH^+]}{[Q]} = 1$, at ⅓ neutralization $\frac{[QH^+]}{[Q]} = 2$ and at ⅔ neutralization $\frac{[QH^+]}{[Q]} = ½$

Therefore, substituting the values of $\frac{[QH^+]}{[Q]}$ in equation (3) $pK_A = pH_{½} + \log 2$; $pK_A = pH_{½} + 0$; and $pK_A = pH_{⅔} - \log 2$.

It should be noted that pK_A and pK_B are interconvertible by means of the combined relations from equations (1) and (2).

$$K_B \cdot K_A = [H^+]\ [OH^-] = K_W$$

or $pK_B = pK_W - pK_A$, where pK_W for pure water is 14.2 at 20 degrees C. In mixed solvents such as alcohol and water, the value of pK_W will be higher, 14.5 and 14.8 for 50 and 75 per cent alcohol, respectively (35).

The acid dissociation constants are employed in describing the "strength" of bases, which are represented by Q as part of the "acid" $[QH^+]$.

The weaker the base the smaller is pK_A and the larger is pK_B.

The method of carrying out electrometric aqueous titrations is simplified by the glass electrode for H^+-ion concentration measurements. Details for conducting such titrations are given by Saunders and Srivastava (34) and by Michaelis (35). The range of narcotic pK_A values is 8.97 – 3.76. A number of pK's for narcotics have been published by Levi and Farmilo (37), and Kolthoff (36).

Electrometric titrations in glacial acetic acid comprise another extension of the method which is extremely useful for titrating bases which are very weak in aqueous solutions. A recent review of the methods of non-aqueous titrations applied to narcotics and alkaloids (36) showed that papaverine, phenadoxone, pipidone, and narcotine, with pK_A values in water less than 7, did not have sharp inflection points in their titration curves in water, while in glacial acetic acid, titration with perchloric acid yielded sharp end points.

(b) *Polarography* (38)

Polarography is another method dependent upon the measurement of electromotive force and is useful in quantitative and qualitative analysis of narcotics. Polarography detects the presence of certain functional groups (shown in table I, column 3, by label P) which can be either oxidized or reduced according to the following equation:

$$\text{oxidant} + n\,e \longrightarrow \text{reductant}$$

Polarography combines electrolysis with the measurement of electromotive force. The electrolysis is always of short duration and never complete, if the electric current is prevented from altering by use of a microelectrode in a large volume of solution, the other electrode being kept large and unpolarizable. Polarography is concerned with electrode reactions, involving transfer of electrons. The electrode is the cathode when reduction occurs, and if the electrons leave the cathode to reduce the oxidant; and is the anode when oxidation occurs, i.e., electrons leave the solution to enter the anode and leave behind an equivalent amount of the oxidant. During the reactions at the microelectrode the macroelectrode becomes alternately the anode and cathode respectively. The narcotic in solution either is oxidant or reductant, and subsequent products from electrode reaction form an oxidation-reduction system.

The use of polarography in narcotic analysis has been limited although several compounds have chemical groups which are ordinarily capable of entering into reduction-oxidation reactions. These narcotics are shown in table I as being potentially analysable by means of polarography. Berberine, cotarnine, and hydrastinine in pharmaceutical preparations have been determined polarographically by Sentavy (39).

9. Conclusions

Narcotic identifications are usually carried out by means of color and crystal tests. A closer adherence to the classical schemes of organic analysis may be warranted for qualitative narcotic identification. A general scheme of analysis has been proposed in order to introduce the necessary modifications in current methods of narcotic analysis. One shortcoming of current chemical methods is that they change the original narcotic to such an extent that it is not available for further examination. Since some common physical properties are not apparently too useful in the classification step of the proposed analytical procedure, other physical data must be obtained, for complete identification in the classical organic sense. A number of methods based on size, shape, atomic configuration and functional chemical groups of narcotics have been studied and assessed in order to determine their applicability to the special problem of narcotic analysis. Three methods, X-ray powder diffraction, and ultra-violet and infra-red spectrometry, were selected from a larger list of physical methods and have been studied by us extensively, in application to narcotics. These methods will be reviewed in detail in subsequent papers. A number of other physical methods are apparently also useful and will be the subject of still further work.

With regard to specific methods there are two broad, similar uses for ultra-violet spectrophotometry, electrometric titrations and polarographic determinations in narcotic analysis. First, to classify a narcotic into one of four large chemical families, and sometimes restricting it into a smaller subdivision of these families. Second, the methods may be used to determine accurately the amount of the substance present.

Infra-red is most useful in determination of specific chemical functional groups, and with additional data we may be able to eliminate numbers of possible materials, and to select the most likely compound from the list of possibilities.

Raman and fluorescence spectra need to be obtained before the usefulness of these methods can be assessed practically.

A complete crystallographic description appears to be the most desirable way of identifying completely a pure crystalline drug. The most useful single physical method that we have investigated for purposes of narcotic identification is the X-ray diffraction powder method. It has been tested by us successfully in the detection of drugs of doubtful purity obtained from toxicological cases. Optical crystallography is needed in addition to X-ray diffraction for establishing complete and unequivocal identity of a pure organic crystalline phase.

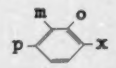
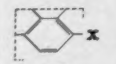
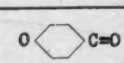
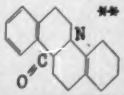
TABLE I

	pyrahexyl, pipidone, isomethadone, phenadoxone	IR, R
	pyrahexyl, mescaline, narceine, ethylnarceine, ecgonine, ethylpethidine, ketobemidone, diarylalkoneamines, isoquinolines	IR, R
	pyrahexyl, opianic acid, mescaline, trichocereine, narceine	IR, R
	iminoethanophenanthrofurans, diarylalkoneamines, alkylpiperidines	IR, R
	meconic acid, pyrahexyl, diamorphine, nalorphine, other iminoethanophenanthrenes	IR, R, UV
	thebaine	IR, R UV
	sinomenine	UV
	iminoethanophenanthrofurans	UV, IR
	thebaine	UV, IR
	meconic and opianic acids, narceine, ecgonine	IR, R, E, P

	opianic acid	IR, R
	methylketobemidone, ketobemidone, propyl and acetoxyketobemidones, cryptopine, protopine, sinomenine, dihydromorphinone and codeinone, metopon, dihydrohydroxycodeinone, acedicone, diarylalkoneamines	IR, R
	ethylmorphine	IR, R
	opianic acid, mescaline, trichocereine, narceine, ethylnarceine, cocaine, narcotine, cotarnine, meconic acid, hydrastinine, dioxyline, papaverine, cryptopine, morphothebaine, racemethorphan, sinomenine, codeine, thebaine, dihydrocodeine, codeinone	IR, R
	benzylmorphine	IR, R
C=O including various types of C=O groups	narceine, ethylnarceine, cocaine, ecgonine, pethidine, ethylpethidine, α-prodine, hydroxypethidine, methyl-, propyl- and acetoxyketobemidone, diarylalkoneamines, iminoethanophenanthrofurans (keto series), narcotine, cryptopine, protopine, sinomenine, diamorphine, α-monoacetylmorphine, methadylacetate	IR, R, UV, E, P

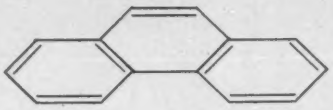
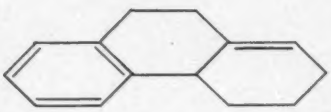
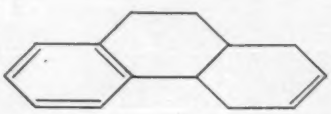
TABLE I (*continued*)

-OH (phenolic)	pyrahexyl, hydroxypethidine, methylketobemidone, ketobemidone, laudanine, protopine, apomorphine, morphothebaine, thebenine, racemorphan, sinomenine, morphine, dihydromorphine, codeine, metopon, morphine-N-oxide, nalorphine, pseudomorphine, etc.	IR, R UV, E, P
-OH (alcoholic)	ecgonine, morphine, codeine, dihydromorphine, dihydrohydroxycodeinone, ethylmorphine, benzylmorphine, α-monoacetylmorphine, morphine-N-oxide, nalorphine, pseudomorphine, etc.	IR, R, UV, E, P
-OH	mescaline, arylpiperidines, ketobemidone, laudanine	IR, R, UV, E
	narceine, cocaine, ecgonine, pethidine, ethylpethidine, α and β-prodine, hydroxypethidine, and other arylpiperidines, phenanthrenes	IR, R, E
$-NH_2$	mescaline	IR, R, E
	methadone, isomethadone, methadyl acetate, trichocereine, etc.	IR, R, E
$-N-CH_3$	morphine, codeine, thebaine, etc.	IR, R, E, UV
$-[(-N-CH_3)]^+$	nalorphine	IR, R, E
-N-R	cotarnine, hydrastinine	IR, R, P, E

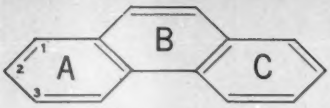
-N=O	morphine-N-oxide	IR, R, P, E
	phenadoxone	IR
	aryls; opianic acid, pethidines, diarylalkoneamines, benzylisoquinolines, etc.	IR, R, UV
 and  condensed rings	opianic, pyrahexyl, mescaline, narceine, ethylnarceine, hydroxypethidine, ketobemidone, methyl-, ethyl- and propyl-, acetoxyketobemidones, narcotine, papaverine, dioxyline, cryptopine, apomorphine, morphothebaine, racemorphan, morphine, codeine, neopine, thebaine, dihydromorphine and codeine, dihydromorphinone and codeinone, metopon, ethyl-, benzylmorphine, nalorphine, morphine-N-oxide, acedicone, etc.	IR, R, UV
	meconic acid	IR, P
condensed furan	iminoethanophethrofurans; like morphine, codeine, thebaine, dihydro-, morphine and codeine, morphinone and codeinone, metopon, morphine-N-oxide, nalorphine, acedicone, pseudomorphine, etc.	IR, R, UV
	pyrahexyl, and other marihuana principles	IR, R, UV
	cryptopine, protopine	IR, R UV

*condensed pyran ** 10-membered ring

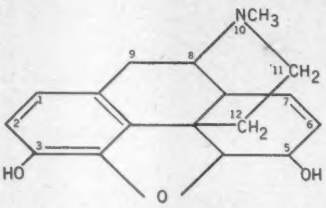
TABLE II

CHROMOPHORE	COMPOUND
	thebenine
	apomorphine morphothebaine
	thebaine
	neopine
	sinomenine, morphine, codeine, ethylmorphine, benzylmorphine, diacetylmorphine, morphine-N-oxide, N-allylnormorphine, pseudomorphine, monoacetylmorphine
	acedicone
	racemorphan, racemethorphan, dihydromorphine, dihydrocodeine, dihydromorphinone, dihydrocodeinone, methyldihydromorphinone, dihydrohydroxycodeinone

DETAIL OF STRUCTURE



phenanthrene



morphine

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The Stereochemistry of Morphine

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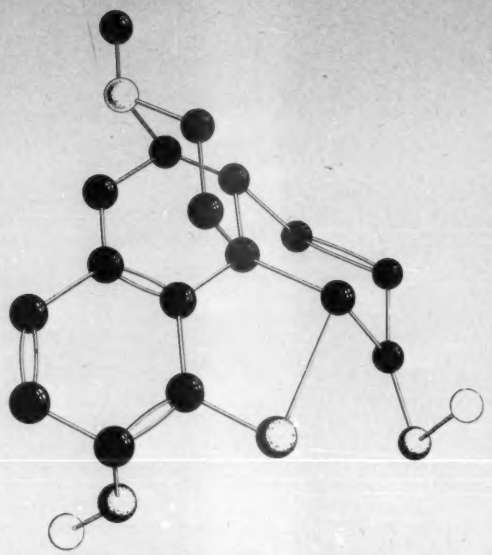
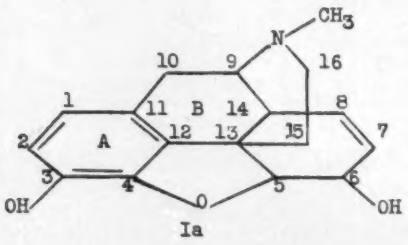


In this review, the fine stereochemistry at the various asymmetric centres in the morphine molecule will be discussed on the basis of degradative evidence. The information gleaned from various synthetic approaches to morphine will also be discussed, in so far as it may elucidate the steric configuration of the alkaloid or of certain of its degradation products. Since it is clearly established that morphine and its methyl ether, codeine, are members of the same stereochemical series, much of the evidence obtained for the configurational relationships in codeine or its degradation products (used primarily because of their greater stability as compared to the corresponding unmethylated compounds) will apply equally to morphine.

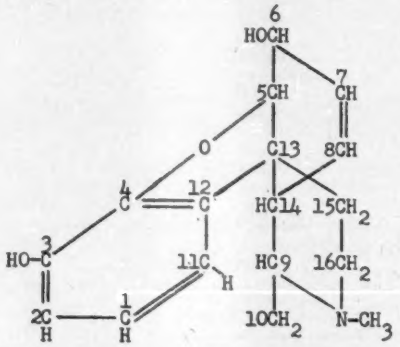


Ia

Morphine has five asymmetric carbon atoms: C_5, C_6, C_9, C_{13}, C_{14} (for the numbering system, see structure Ia). The appearance of the molecule in space may be visualized more readily from the above artist's conception.[1]

[1] The artist's drawing shows the basic skeletal structure of morphine. Most of the hydrogen atoms are not shown. We acknowledge with thanks the co-operation of Mr. Amnon Rubenstein in preparing this drawing.

Emde (1)[2] arranged the atoms of morphine in the manner indicated by structure Ib, in order to emphasize the similarity of the straight chain made up of the five asymmetric centres, to the cyclic forms of aldoses. This formulation is of interest only in that it points out this relationship. It is not useful as a spatial representation of the molecule.

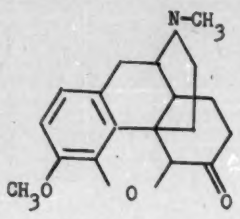


Ib

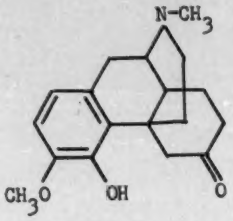
From a study of the optical rotations of certain of the opium alkaloids and their derivatives and employing the principle that the molecular rotation is an additive function of the rotations at the component asymmetric centres, Emde concluded that three of the five asymmetric carbon atoms (C_5, C_6, C_9) rotate the plane of polarized light to the left (—) and the remaining two (C_{13}, C_{14}) do so to the right (+). This work shows that the configuration of morphine is the same as in one of the two cyclic forms of aldoses in which the five asymmetric centres are arranged according to the scheme: (—)C_1; (—)C_2; (+)C_3; (+)C_4; (—)C_5, or according to the inverse scheme: (—)C_1; (+)C_2; (+)C_3; (—)C_4; (—)C_5. Although these rotational contributions (+ or —) have been assigned to the

[2] Arabic figures in parentheses indicate items within the list of references to be found at the end of this article.

asymmetric centres, it must be pointed out that this assignment provides no information as to the actual configurations. Bick (1 a) has recently published a preliminary note in which it is suggested on the basis of rotation displacements that morphine is related to L (+) tartaric acid in its absolute stereochemical configuration.



II



III

Schöpf and Pfeifer (2), on the basis of a study of models, interpreted the fact that dihydrocodeinone (II)[3] is formed exclusively from dihydrothebainone (III) by oxide ring closure at C_8, as indicating that the C_8-O bond is *trans* to the ethanamine bond at C_{13}. The hydrogen at C_{14} was inferred to be *cis* to the ethanamine bond at C_{13} by analogy to the situation prevailing in the 14-hydroxy compound. Since degradation of dihydro-14-hydroxycodeinone (VI) to nitrogen-free material resulted in the formation of a cyclic ether (VII) involving the hydroxyl group at C_{14}, the hydroxyl and the ethanamine bridge must be *cis* to each other (see chart I).

If we assume that the 14-hydroxyl group and the 14-hydrogen in related compounds, possess the same configuration, the hydrogen at C_{14} must also be *cis* to the ethanamine chain.

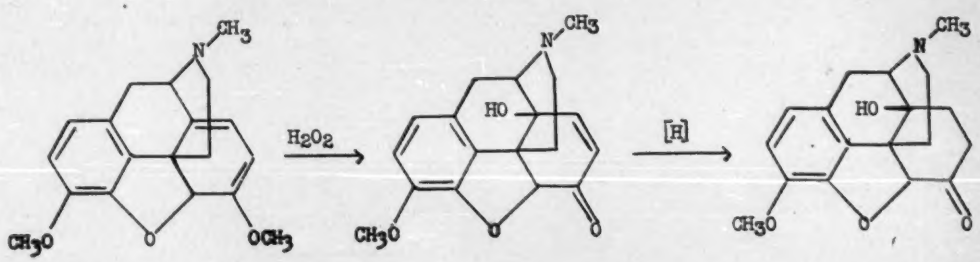
Gulland and Robinson (3) suggested that hydrogen peroxide causes 1,4-hydroxylation of the diene system of thebaine (IV) with subsequent elimination of methanol to form the C_6 carbonyl group.

There is no ironclad proof showing that the C_{14} hydrogen in morphine and codeine has the same configuration as the C_{14} hydroxyl in 14-hydroxycodeinone (V). Schöpf assumed that the probability for identical configuration at C_{14} in both cases was high because hydrogenation of the 8,14 double bond in various compounds of this series, proceeds in only one steric sense. A study of models indicated that when the hydrogen atom at C_{14} is *cis* to the ethanamine bridge a strain-free system can be obtained. Although compounds having the opposite relationship are known (*vide infra*), this reasoning, although not affording conclusive proof of the point, was shown to be correct when later work had been carried out by Rapoport and co-workers, who conclusively clarified the configurational relationships of all the asymmetric centres of the morphine molecule.

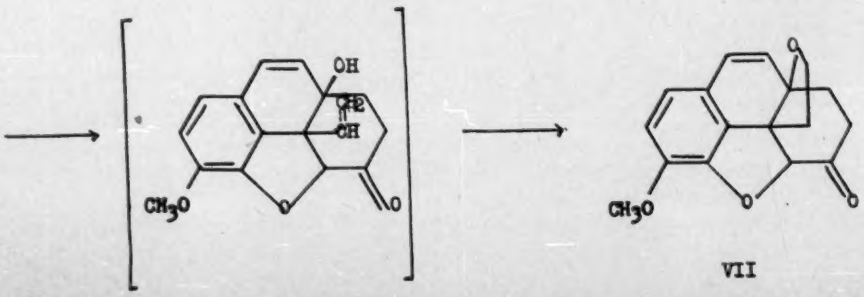
Rapoport and Payne (4) undertook to determine by absolute methods, the relative configurations at the various asymmetric carbon atoms of morphine.

[3] Roman numerals in parentheses indicate reference to structures to be found within the charts.

Chart I



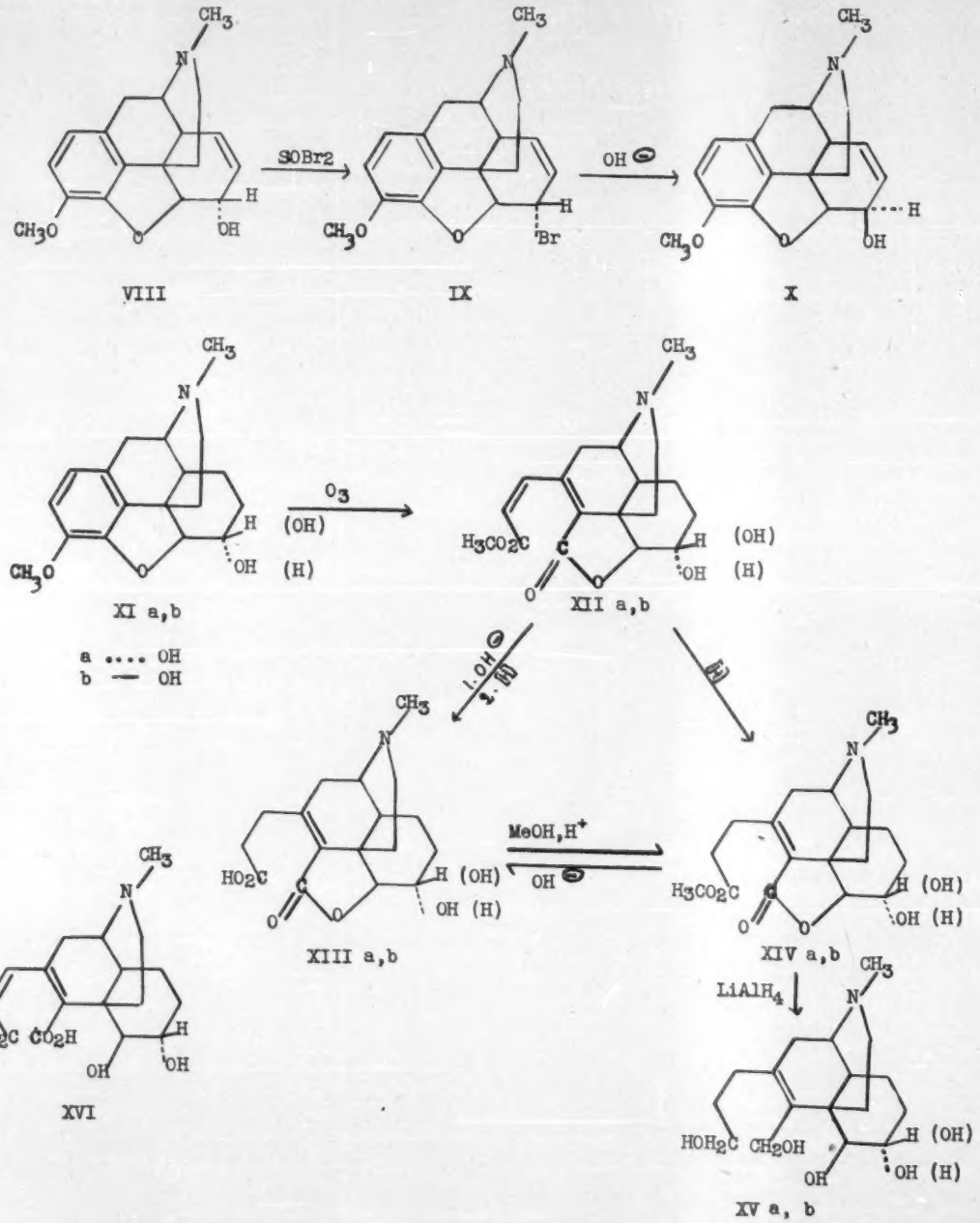
IV V VI



VII

To determine the relative configuration at C_5 and C_6 the oxide ring was opened at C_4 rather than in the usual manner at C_5 (chart II). A pair of vicinal glycols (at C_5 and C_6) would result from dihydrocodeine (XIa) and dihydroisocodeine (XIb), respectively, and their configuration could be determined by the usual reagents used for differentiation between *cis* and *trans* diols.

Chart II



Dihydrocodeine (XIa) was prepared by reduction of codeine (VIII) and dihydroisocodeine (XIb) was prepared in 35 per cent over-all yield by reduction of isocodeine (X), which in turn was obtained from codeine (VIII) by treatment with thionyl bromide to yield bromocodide (IX)[4] followed by hydrolysis to the alcohol. The transformations carried out with the isomeric pair, dihydrocodeine and dihydroisocodeine are summarized in chart II.

Dihydrocodeine (XIa) and dihydroisocodeine (XIb) differ only in the relative configuration of the hydrogen atom and the hydroxyl group at C_6. In the former, the hydroxyl is represented by the dotted bond (below the plane of the paper) and the hydrogen by the solid bond, while in the latter compound, the reverse relationship holds.

Ozonolysis of dihydrocodeine (XIa) and dihydroisocodeine (XIb), in turn, yielded ozodihydrocodeine (XIIa) and ozodihydroisocodeine (XII) respectively. Hydrolysis of both the methyl ester and lactone groups of ozodihydrocodeine (XIIa) yielded dihydromorphinic acid (XVI), which was too unstable for further work but hydrolysis and reduction of the hydrolysate gave the stable, tetrahydromorphilactonic acid (XIIIa). The latter could be prepared alternatively by first reducing the methyl tetrahydromorphilactonate (XIVa) with subsequent saponification to the acid (XIIIa). The ester could be regained by Fischer esterification.

Tetrahydromorphitetrol (XVa) was obtained by reduction of the morphilactonate (XIVa) with lithium aluminum hydride. Since the C_5-O bond was not broken at any step of these transformations, the configuration at this point remains unaffected and the compound ultimately obtained (XVa) has a pair of vicinal hydroxyl groups at C_5 and C_6 with the original configurations at these carbon atoms retained.

The epimeric tetrol (XVb) was prepared by the same sequence of reactions carried out with dihydroisocodeine (XIb), and the tetrahydro-α-isomorphitetrol (XVb) ultimately obtained, differed from tetrahydromorphitetrol (XVa) merely in configuration at C_6.

It has been shown (5) that *cis*-1,2-diols are oxidized more rapidly with lead tetraacetate, than the corresponding *trans*-1,2-diols. Both tetrols (XVa and XVb) consumed one mole of lead tetraacetate. The α-isomer required more than six hours for consumption of this quantity whereas the other isomer required two hours, i.e., in the dihydrocodeine series the consumption was about thrice as rapid as in the dihydroisocodeine series.

Since an exception to the apparent rule that *cis* glycols are more rapidly oxidized than their corresponding *trans* isomers had been reported (6), the effect of the glycols on the pH of a boric acid solution was also examined. It has been shown (7), that the pH of 0.1M boric acid is changed to a greater extent by successive additions of a *cis*-diol than by a *trans*-diol. When this test was applied to the picrate of tetrahydromorphitetrol (XVa) (*cis* series) the effect on the pH of 0.1M boric acid was an over-all change in the pH from 5.20 to 4.01 while for the picrate of tetrahydro-α-isomorphitetrol (XVb) (*trans* series), the over-all change was from 5.20 to 4.85.

The conclusion was therefore reached by Rapoport and Payne, that in tetrahydromorphitetrol (derived from morphine) the hydroxyl pair at C_5 and C_6 are *cis* and in the α-isomer (epimeric at C_6) the hydroxyl groups are *trans* to each other. Therefore, in morphine itself, the C-O bonds at C_5 and C_6 are *cis* and in α-isomorphine they are *trans*.

Let us now consider the relative configuration at C_6 and C_{13}. Rapoport (8) has shown that on Hoffmann degradation of dihydrocodeine (XIa), an appreciable amount of methylation of the C_6-hydroxyl group takes place. This observation would indicate the occurrence of intramolecular methylation of the hydroxyl group by the quaternary ammonium ion XVIIIc,d which is an intermediate in the degradation reaction. This led to the idea that if the hydroxyl group at C_6 and the ethanamine chain at C_{13} were situated favorably in space, a cyclic ether (XXIII) might be formed as one of the degradation products. Obviously, only the compound in which these groups are *cis*, would fit the spatial requirements for the formation of the cyclic ether anchored at C_6 and C_{13}.

Accordingly, dihydrocodeine (XIa) and dihydroisocodeine (XIb), respectively, were subjected to the conditions of the Hoffmann exhaustive methylation and degradation reaction, and the complex mixture of products resulting in each case was separated into a basic fraction (XXIa, XXIb, XXIIa, XXIIb) and a neutral fraction (XIXa, XIXb, XXa, XXb). As will be seen below, the neutral fraction resulting from dihydroisocodeine contained also a small amount of 6-codiran (XXIII). Further, each of these fractions was separated into an alcoholic and non-alcoholic component through formation of the *p*-phenylbenzoyl ester of the alcoholic material, followed by purification of this material by sublimation (see chart III).

In the case of dihydrocodeine (XIa) the basic material consisted of the methine (XXIa) and its 6-methoxy-derivative (XXIIa). The neutral material was made up of 6-α-hydroxy-13-vinyl-octahydromethylmorphenol (XIXa) and the corresponding 6-α-methoxy compound (XXa).

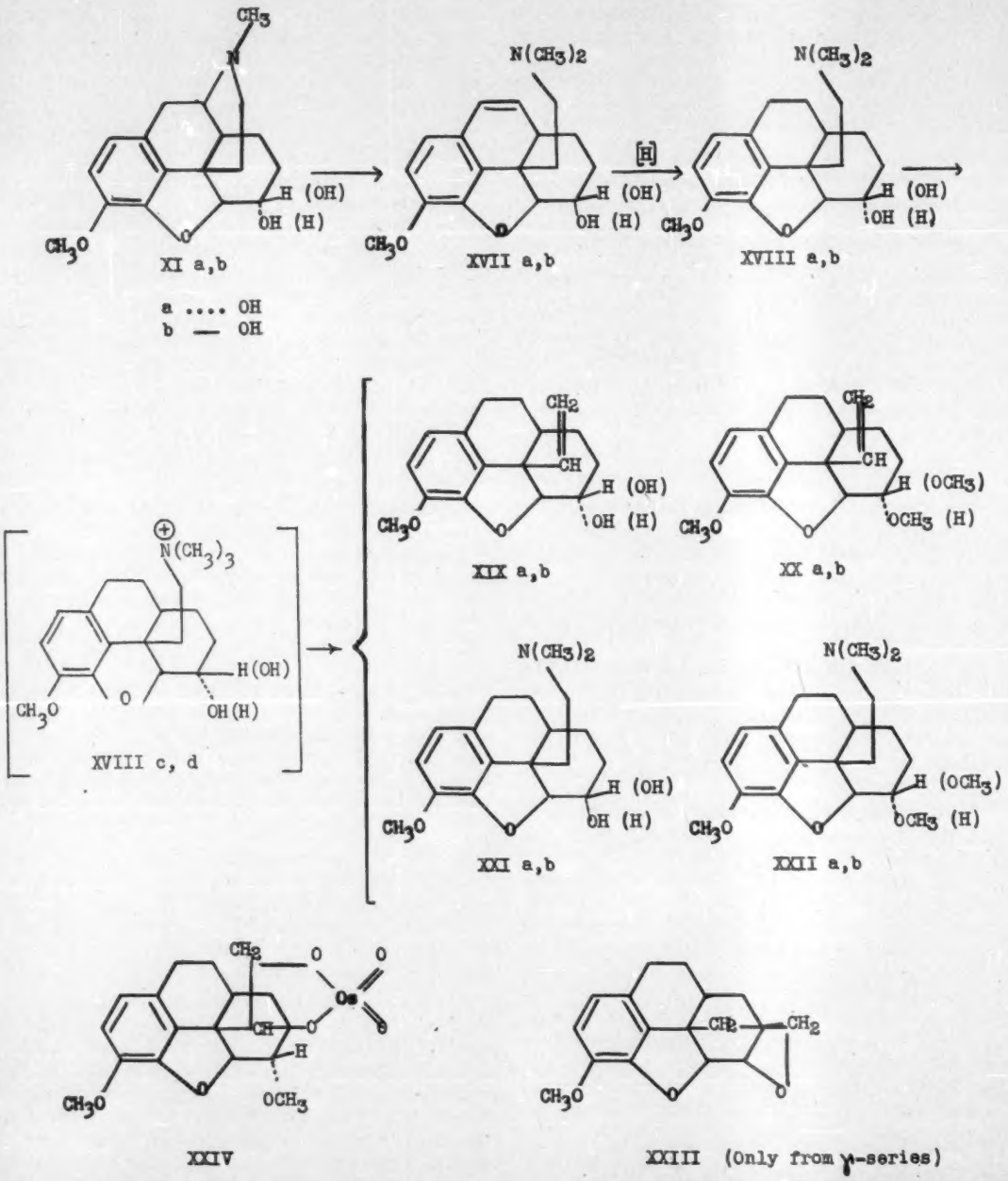
Any cyclic ether (XXIII) would be expected to be present in the non-alcoholic fraction of the neutral material, accompanying XXa. Its absence in this case was shown by quantitative hydrogenation experiments and methoxyl determinations which showed that there was no non-olefinic or non-methoxylated material present. Moreover, in order to separate any suspected saturated material from olefinic compounds, hydroxylation with osmium tetroxide was carried out. The olefinic fraction formed the

[4] The formulation of IX in chart II is uncertain, as in bromocodide, the bromine atom may be at C_8 and the double bond may be Δ^6 – rather than Δ^7-. However, even before unequivocal evidence is furnished regarding this point, the structure of X is certain.

osmate of the diol (XXIV) which was sufficiently insoluble to effect separation of the olefinic material. This reaction served to confirm the absence of saturated cyclic ether. This evidence indicated that in dihydrocodeine (and therefore in codeine and in morphine), the hydroxyl group at C_6 is *trans* to the ethanamine chain at C_{13}.

Confirmation was obtained from the results of the reaction sequence carried out with dihydroisocodeine (XIb). A similar mixture of basic and neutral frac-

Chart III



tions was obtained for the 6-γ-isomers. In this case, however, application of the osmium tetroxide hydroxylation procedure separated the vinyl-6-γ-methoxy compound (XXb) from the cyclic 6-codiran (XXIII). It was concluded, therefore, that in the isocodeine series (6-γ-series) the hydroxyl group at C_6 and the ethanamine chain at C_{13} are *cis* with respect to one another.

It is unfortunate that no more than a 2 per cent yield of 6-codiran was isolated from this series of reactions and that the relative proportions of isomeric degradation products were not dramatically different. Thus, it might be expected by the same steric argument used above, that the proportion of methyl ether be greater in the case of the γ-isomer than in that of the α-isomer. The total yield of material unmethylated at C_6 was 64 per cent in the α-series and 34 per cent in the γ-series. Similarly, the total yield of material methylated at C_6 was 34 per cent in the α-series and 61 per cent for the γ-isomers in addition to a 2 per cent yield of 6-codiran in the latter case. The trend is therefore in the expected direction and the assignment in morphine of a C_6-C_{13} *trans*-relationship seems well established.

Returning now to the *cis* relationship earlier established for the hydroxyl group at C_6 and the C_5-O bond, in morphine, and adding the fact that the C_6-hydroxyl in morphine is *trans* to the ethanamine chain at C_{13}, it follows that the hydrogen atom at C_5, the hydrogen atom at C_6 and the ethanamine chain at C_{13} must all be *cis* to each other. A further corollary to the situation prevailing at C_5 and C_{13} is the conclusion that the five-membered oxide ring must be fused in the *cis* manner. The ethanamine bridge joining C_9 and C_{13} must be *cis* since it is impossible in the morphine system to form a six-membered ring across these positions in the *trans* configuration. Protiva and Sörm (9) have shown that it was impossible to form a lactam from *trans*-3-amino-cyclohexaneacetic acid but Cronyn (10) and Ginsburg (11) have shown that the *cis* lactam is readily formed from the isomeric *cis*-3-amino-cyclohexaneacetic acid or from the ethyl ester of the *cis* acid.

It remained, therefore, to relate the configurations at C_{13} and C_{14} in order to complete our knowledge about the fine stereochemistry of the morphine molecule. Rapoport (12) has proven the configurational relationship at these centres in the manner summarized in chart IV.

Thebaine (IV) was reduced to dihydrothebainone (III) and after two Hoffmann degradations through the intermediates XXV and XXVI, the 13-vinyl compound presumably formed, yielded the cyclic ether through reaction of the vinyl group with the free hydroxyl group at C_4, so that the product isolated was thebenone (XXVII). Treatment with an alkyl nitrite in the presence of potassium *t*-butoxide gave 5,7-dioximino-thebenone (XXVIII) which on treatment with *p*-toluenesulfonyl chloride in

Chart IV

A. Normal series

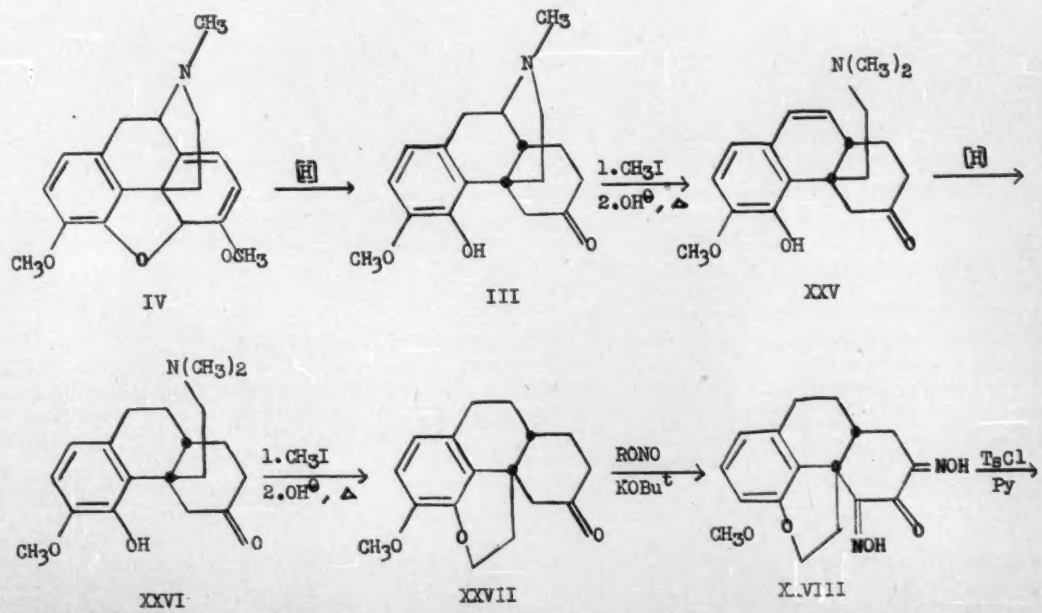
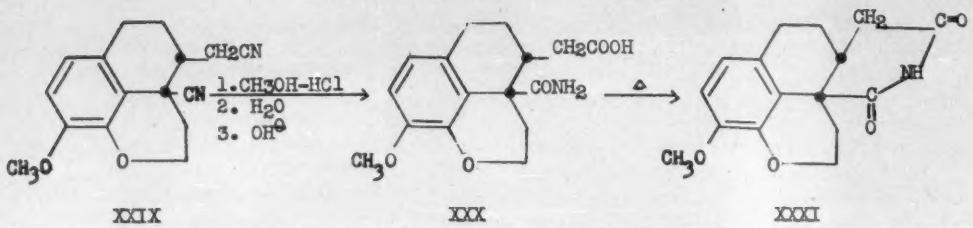
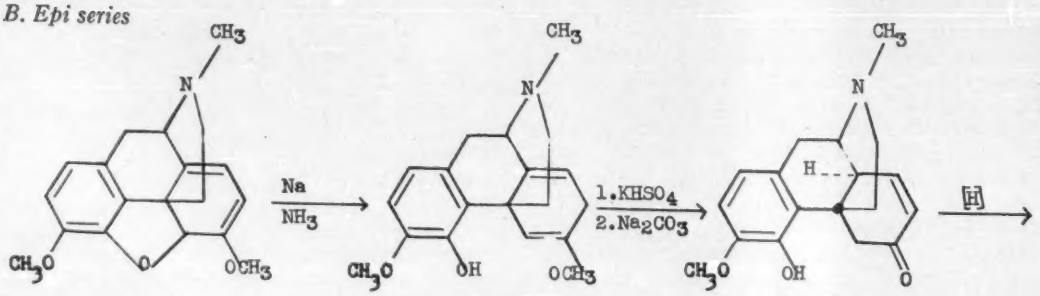


Chart IV (*continued*)

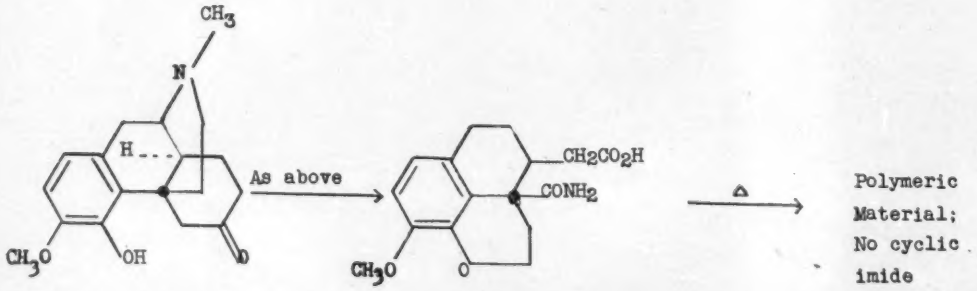


XXIX XXX XXXI

B. Epi series



IV XXXII XXXIII



XXXIV XXXV

pyridine yielded the dinitrile XXIX. Saponification of the less hindered cyanomethyl group to the acetic acid and further saponification of the hindered nitrile group to the amide was accomplished in stepwise fashion and heating of the resulting monoacid-monoamide XXX, yielded the cyclic imide XXXI since in this series the carboxymethyl and amide groups are in the *cis* relationship, no reactions having been carried out in the series of transformations which might have permitted inversion at the original centres of C_{13} and C_{14}.

β-Dihydrothebainone (XXXIV), in which rings B and C are locked in the *trans*-octalin configuration, was prepared by Birch reduction (sodium in liquid ammonia) of thebaine (IV) followed by treatment of the reduction product XXXII with potassium acid sulfate which effects the conversion to β-thebainone (XXXIII). Reduction of β-thebainone yielded β-dihydrothebainone (XXXIV) which was transformed as in the case of the normal series (C_{13}-C_{14} *cis*), to the corresponding *trans*-monoacid-monoamide XXXV. When the latter was heated, no cyclic imide was obtained. Only polymeric material was formed.

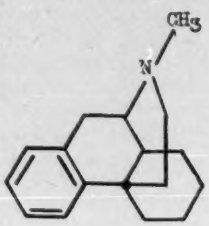
On the basis of these transformations, it has been shown that the long-presumed *cis* relationship of the hydrogen atom at C_{14} to the ethanamine bridge at C_{13}, indeed holds true in morphine.

Stork (13) has brilliantly correlated and interpreted a number of other reactions in morphine chemistry in the light of present-day knowledge of the reaction mechanisms involved. These reactions confirm the above steric assignments to the various asymmetric centres of morphine. For further details the reader is referred to Stork's review.

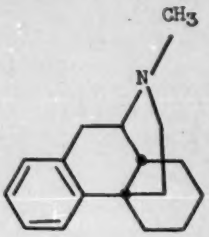
* * *

The synthetic investigations which have been carried out due to the interest in the synthesis of morphine have produced a number of interesting stereochemical points in relation to morphine and certain of its degradation products.

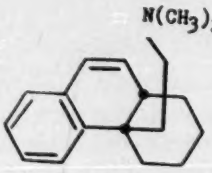
The total synthesis of morphine has been accomlished recently by Gates and co-workers (14) as the culmination of effort expended by many organic chemists for several decades. The synthetic approaches to the morphine molecule have been numerous and have been reviewed by Stern (15). In this review only a number of stereochemical points omitted in Stern's paper will be discussed.



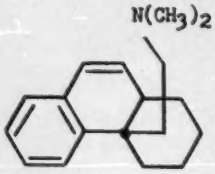
XXXVIII



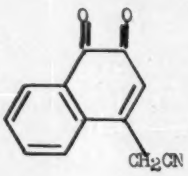
XXXIX



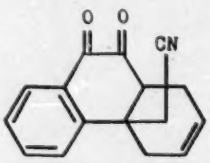
XL



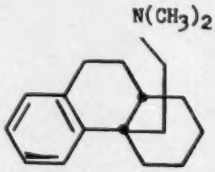
XLI



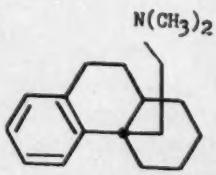
XXXVI



XXXVII



XLII



XLIII

Gates and Newhall (14) prepared *trans*-4a-cyanomethyl-1, 4, 4a, 9, 10, 10a-hexahydro-9,10-diketophenanthrene (XXXVII) by means of a Diels-Alder reaction of 4-cyanomethyl-1,2-naphthaquinone (XXXVI) with butadiene. Despite the stereospecificity of the Diels-Alder reaction, which would be expected to lead to a *cis* compound, only the adduct XXXVII in which the hydrogen atom at C_{10a} and the cyanomethyl group at C_{4a} were in the *trans* relationship, was formed, due to the presence of the carbonyl group adjacent to the ring junction, as shown by further synthetic conversion to N-methyl-isomorphinane (XXXVIII) in which rings B and C are *trans*-locked. In *N*-methyl-morphinane (XXXIX) prepared by Grewe and co-workers (16) and by Ginsburg and Pappo (17), rings B and C are *cis*-locked. These two tetracyclic tertiary amines yield isomeric dihydrodesbases (XLII and XLIII) after Hoffmann degradation and reduction of the resulting desbases (XL and XLI).

Belleau (18) has synthesized the *trans*-dihydrodesbase XLIII by Wagner rearrangement of methyl 2-spirocyclopentanotetral-1-ol-1-acetate (XLIV) to the tetracyclic lactone XLV (see chart V). The latter product was reduced with lithium aluminum hydride to give the diol XLVI which could be dehydrated to yield a mixture of unsaturated alcohols (XLVII and XLVIII). Reduction of this mixture followed by conversion to the bromide by means of phosphorous tribromide and reaction with dimethylamine gave a product from which only the *trans*-dihydrodesbase, *trans*-4a-β-dimethylaminoethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (XLIII), was isolated in pure form. The product was identical with the dihydrodesbase XLIII obtained by Gates (14) from *N*-methyl-isomorphinane (XXXVIII).

Alternatively, the exclusive synthesis of the *cis*-dihydrodesbase XLII by Ginsburg and Pappo (17)

is of interest, particularly in view of the fact that it was obtained from *trans*-1,2,3,4,4a,9,10,10a-octahydro-4-keto-phenanthrene (LIV).

Michael condensation of 2-aryl-cyclohex-2-enones with donors containing reactive methylene groups, proceeds in high yield. For example, 2-phenyl-cyclohex-2-enone (XLIX) with dibenzyl malonate in the presence of potassium *t*-butoxide affords the adduct L, which upon hydrogenolysis and decarboxylation yields *trans*-3-keto-2-phenyl-cyclohexaneacetic acid (LI). The configuration of the product was shown by Clemmensen reduction of this keto-acid to the known *trans*-2-phenyl-cyclohexaneacetic acid (LII). (17, 19). The keto-acid (LI) can be cyclized to yield *trans*-1,2,3,4,4a,9,10,10a-octahydro-4,9-diketophenanthrene (LIII) in a reaction which still maintains the existing stereochemistry at C_{4a} and C_{10a}. Chart VI summarizes these reactions and the further utilization of LIII in the synthesis of the *cis*-dihydrodesbase (XLII).

Cyanoethylation of the *trans*-monoketone LIV, obtained by catalytic reduction of the *trans*-diketone LIII, yields exclusively the *cis*-4a-β-cyanoethyl derivative LVI. This product was converted to the *cis*-dihydrodesbase, *cis*-4a-β-dimethylaminoethyl-1, 2,3,4,4a,9,10,10a-octahydrophenanthrene by a series of simple transformations shown in chart VI. The cyanoethylation reaction which converts a *trans*-locked octalin system to one having the *cis*-juncture can be readily understood from the mechanism of the Michael condensation which is believed to proceed through the enolate ion (LVa) or the carbanion (LVb) in which the *trans* configuration no longer obtains. It is evident that under the alkaline conditions of the Michael condensation, the *cis*-alkylation product is more stable than the *trans*-isomer.

Another stereochemical point of interest in this field concerns the preparation of *N*-methyl-morphinane (XXXIX) from the intermediate LVII. The reaction sequence involved is summarized in chart VII.

The 4-ethylene glycol ketal of *trans*-1,2,3,4,4a,9, 10,10a-octahydro-4,9-diketophenanthrene (LVII) was treated with *n*-amyl nitrite in the presence of sodium ethoxide to yield the 10-oximino-derivative LVIII. Catalytic reduction of this compound in the presence of hydrochloric acid afforded two isomeric amine hydrochlorides (LIX) and (LX), presumably differing in configuration at C_{10a}. The more abundant of these (LX) was treated with the acid chloride of acetylglycollic acid to give the amide LXI, which on attempted ketalization, surprisingly cyclized to form the diketolactam LXII. The latter was converted, as shown in chart VII, to *N*-methylmorphinane (XXXIX) having the *cis*-octalin configuration. Here again, we are dealing with a case in which the

Chart V

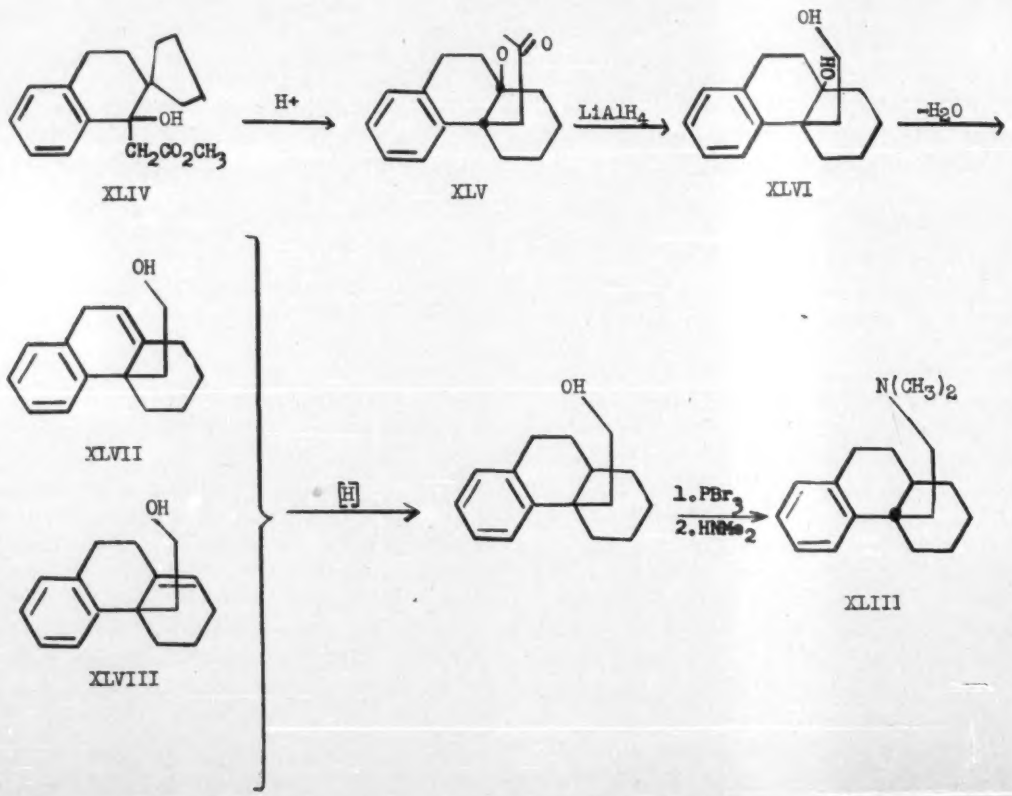
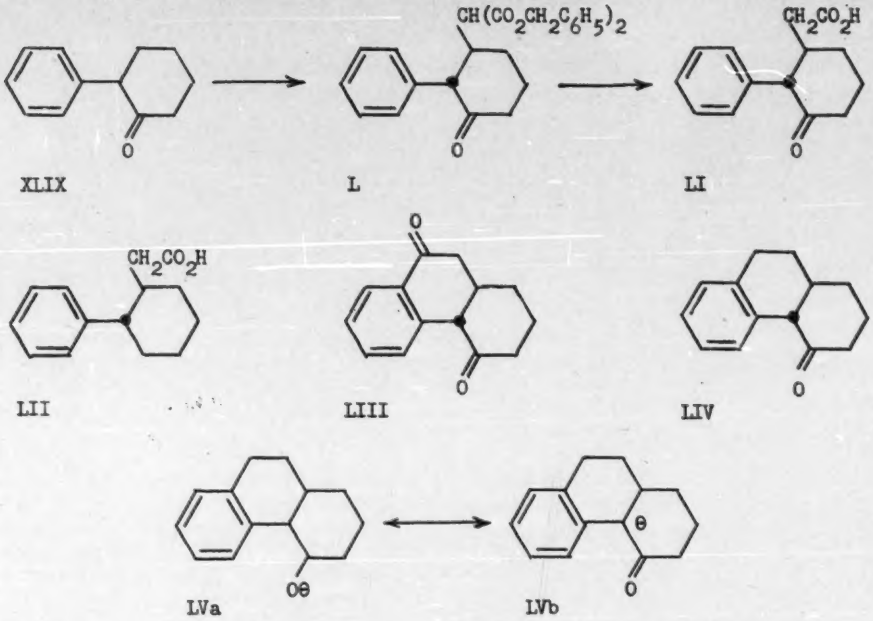


Chart VI


CH(CO2CH2C6H5)2
CH2CO2H
O
XLIX
L
LI
LII
LIII
LIV
Oθ
θ
LVa
LVb

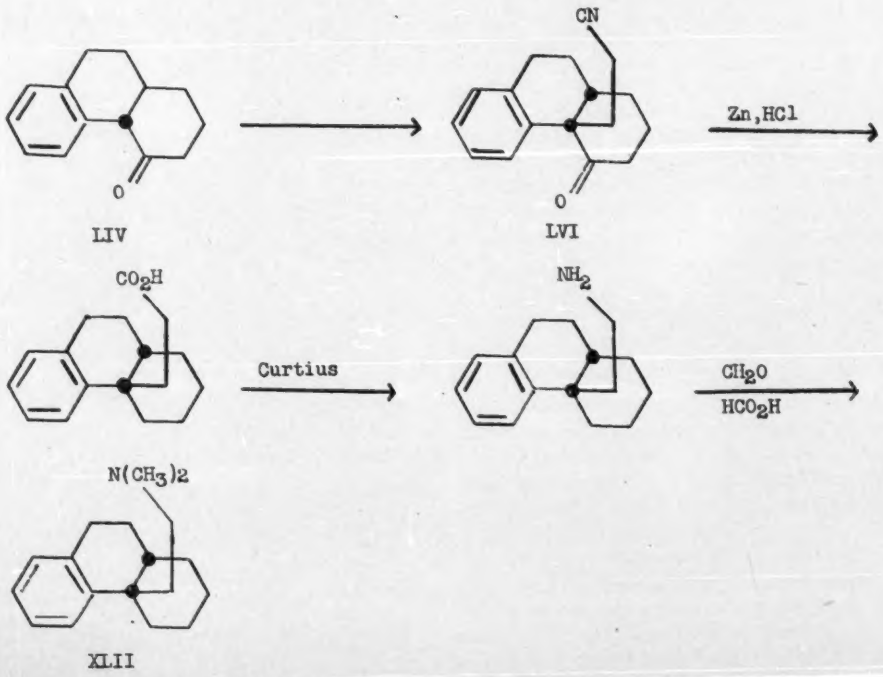
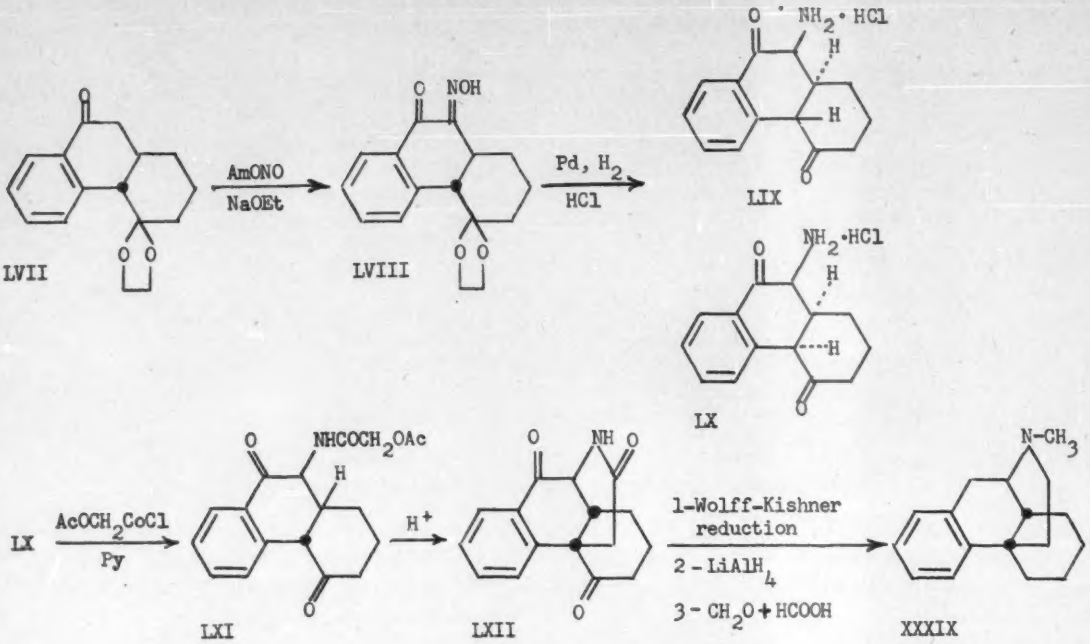

CN
Zn,HCl
LIV
LVI
CO2H
NH2
Curtius
CH2O
HCO2H
N(CH3)2
XLII

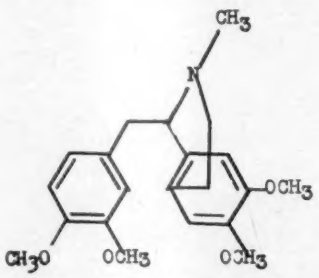
Chart VII



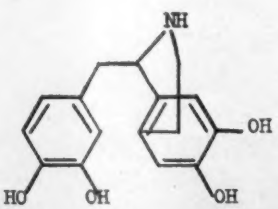
unique cyclization takes place in only one steric sense. Although the mechanism of the cyclization reaction is not known, the lactam of the morphinane rather than the isomorphinane configuration, is the exclusive product. Since only epimerization of the hydrogen atom at C_{4a} is possible in LX and a *cis*-ring junction is obtained in the resulting lactam, it may be deduced that LX has the structure shown, in which the amino group at C_{10} is equatorial. This would be expected to be the stable conformation of the amino group in a compound with *trans*-ring junction.

Also worthy of note, stereochemically, is the cyclization reaction discovered by Grewe (16) in which a product of preponderantly *cis* configuration is formed at C_{13}-C_{14}.

In 1928, Robinson (19) proposed a possible biogenetic relationship between the morphine group of alkaloids and those of the 1-benzylisoquinoline group such as laudanosine (LXIII). The biogenetic conversion of a completely demethylated laudanosine precursor (LXIV) to morphine, requires the formal addition of two hydrogen atoms followed by the loss of the elements of one molecule of water. Robinson's hypothesis is extremely attractive since laudanosine (LXIII) can be formed by simple methylation of the precursor LXIV and the conversion of the latter to morphine involves reactions, for which most probably, enzyme systems exist in the plant.

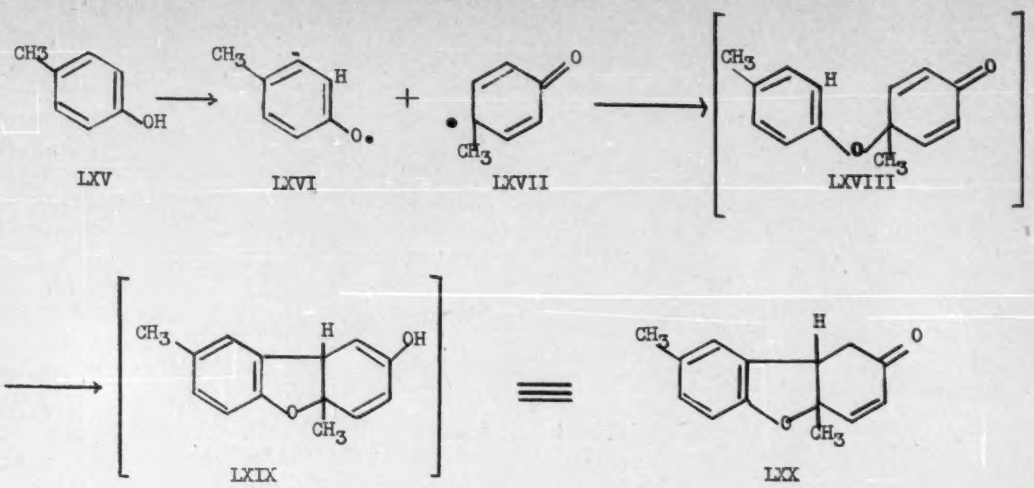


LXIII



LXIV

Chart VIII



Schöpf has recently published a modified biogenetic scheme which relates the morphine alkaloids to the 1-benzyl-isoquinoline group (20). This scheme is based on the analogy to the dehydrogenation reaction, investigated by Pummerer and co-workers (21), in which *p*-cresol (LXV) is converted to the angularly substituted furan derivative LXX, presumably as shown in chart VIII.

In this formulation, it is suggested that *p*-cresol (LXV) gives a radical which reacts partly in the aryloxy form LXVI and partly in the γ-keto-methyl form LXVII, so that when the free valences unite to give LXVIII the hydrogen atom *ortho* to the oxygen in the aryloxy portion of LXVIII adds intramolecularly 1,4 to the ends of the enone system in the γ-keto-methyl portion to give the intermediate LXIX. LXIX is immediately transformed to the stable LXX by ketonization.

Analogously, Schöpf visualizes an intermediate LXXI differing slightly from Robinson's precursor, which must be dehydrogenated to the biradical LXXIIa or LXXIIb. In this case, when the free valences unite intramolecularly, we obtain by 1,6-addition to the ends of a dienone system which differs from the *p*-cresol case in that it contains an α-keto-methyl system (see LXXIIb), the hypothetical precursor LXXIII. This formulation is summarized in chart IX. It will be seen from chart IX that the

Chart IX

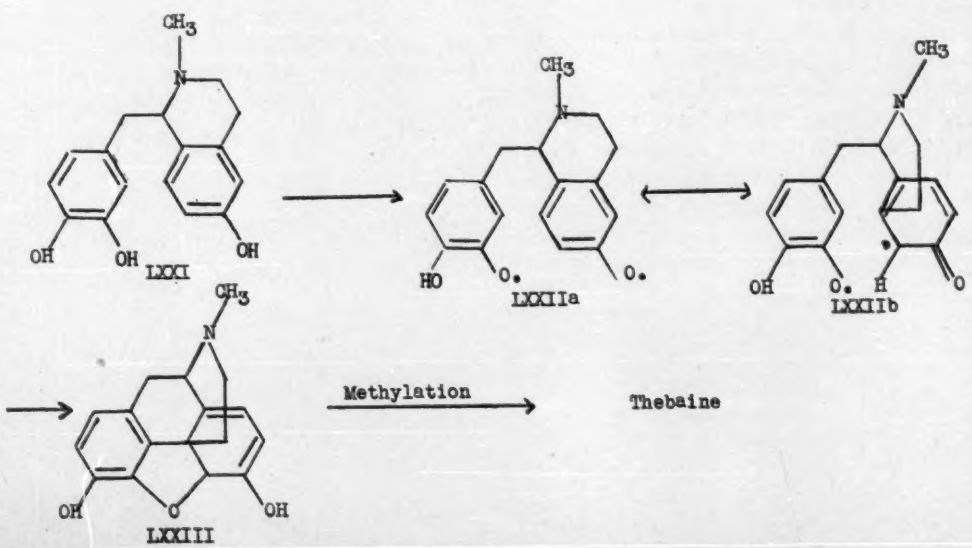
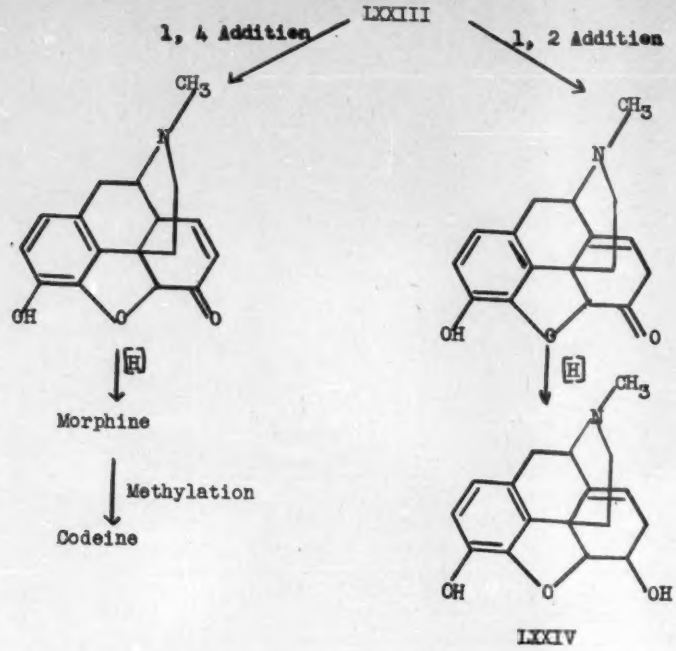


Chart IX (*continued*)

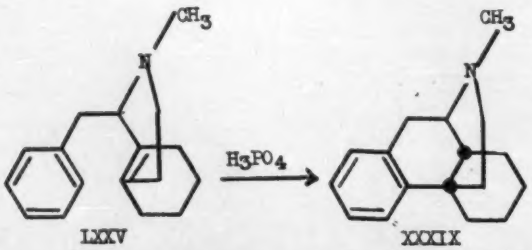


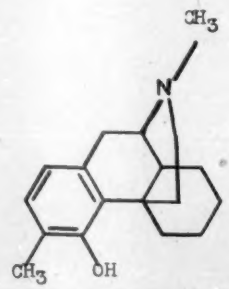
precursor LXXIII can very easily afford morphine, codeine, thebaine or neopine (LXXIV).

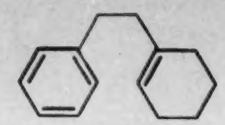
For the difficulties involved in the experimental testing of this biogenetic hypothesis, the reader is referred to Schöpf's paper (20).

In all the synthetic approaches to morphine, the nearest to the presumed biogenetic route, is that of Grewe (16). Although this approach culminated in the very elegant and unique cyclization in which the morphine skeleton was formed from a 1-benzyl-octahydroisoquinoline, the reactions were not carried out under simulated physiological conditions. The preponderantly stereospecific synthesis of *N*-methylmorphinane from 1-benzyl-*N*-methyloctahydroisoquinoline (LXXV) by Grewe produced this compound in 50 per cent yield. A picrate of another isomeric substance was formed only in small amount. It was later shown by Gates (14) that this substance was identical with the picrate of *N*-methylisomorphinane.

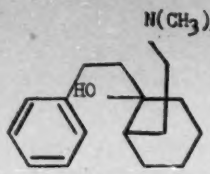
Tetrahydrodesoxycodeine (LXXVI), identical with that obtained from natural sources was also prepared by Grewe and his co-workers (16), employing the same acid cyclization method in which the addition of a hydrogen from the aromatic ring across the tetra-substituted double bond took place to yield the *cis*-octalin structure prevailing in the natural product.



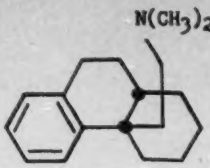




LXXVII



LXXVIII



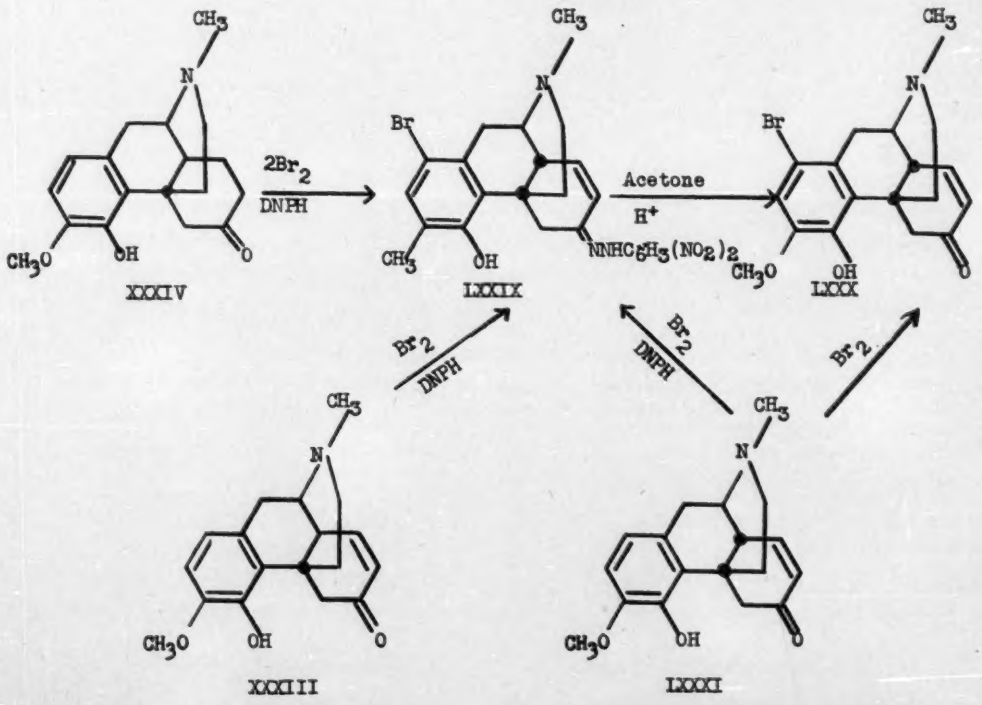
XLII

It is clear that in order to obtain the natural, *cis*-octalin, the cyclization mechanism must involve *trans* addition of the hydrogen atom to the tetra-substituted double bond. In other known cases, such as the cyclization of β-phenethylcyclohexylene (LXXVII) mixtures of *cis* and *trans* products are obtained (22). This apparently depends upon the stability of the carbonium ion intermediates involved in this type of cyclization and it is noteworthy that despite the fact that there appears to be no great difference in stability when Fisher-Hirshfeld models of *N*-methylmorphinane and *N*-methylisomorphinane are studied, the *cis* isomer is formed in this case preponderantly. Analogously, the *cis*-dihydrodesbase (XLII) could be obtained by treatment of the amino-alcohol LXXVIII with syrupy phosphoric acid which effects dehydration followed by cyclization.

The final steric point which must be discussed is the remarkable isomerization of the *trans*-C_{13}-C_{14} system to the isomeric *cis* system during the course of Gates' work on the total synthesis of morphine. The reactions involved are summarized in chart X.

When β-dihydrothebainone (XXXIV) was brominated with two moles of bromine followed by treatment with 2,4-dinitrophenylhydrazine, a dinitrophenylhydrazone LXXIX, was obtained. This derivative was identical with the 2,4 dinitrophenylhydrazone which results from β-thebainone (XXXIII) or from thebainone (LXXXI) by the action of 2,4-dinitrophenylhydrazine in acetic acid with subsequent bromination.

Chart X



XXXIV LXXIX LXXX

XXXIII LXXXI

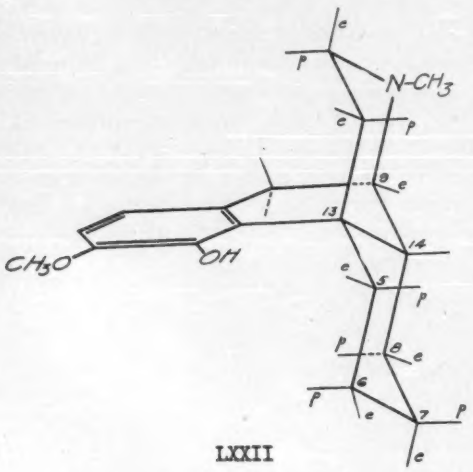
The epimerization at C_{14} took place so readily that the 2,4-dinitrophenylhydrazone of β-thebainone could be obtained only by minimizing contact of the compound with acid. The abnormally high rotation of Δ^7-6-ketone-dinitrophenylhydrazones of the *cis* series as compared to that of derivatives of the *trans* series could be used to follow the progress of the epimerization. The difference in molecular appearance of *cis* and *trans* compounds of this type is illustrated in structures LXXXII and LXXXIII which are reproduced through the courtesy of Dr. Marshall Gates.

It may be seen that each of the approaches to the morphine structure has produced some unique or remarkable reaction. As in the case of many natural products, the interest in morphine has led to the development of new methods and reactions of interest to chemistry as a whole.

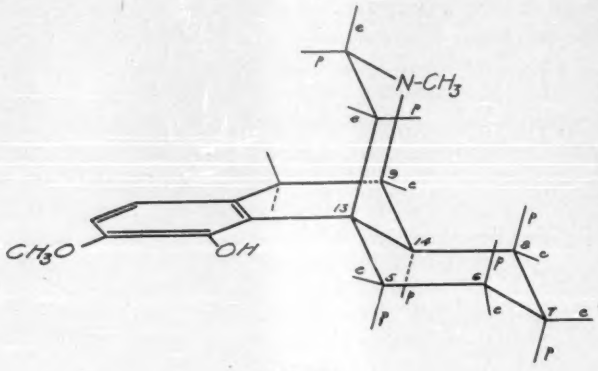
The variety of rearrangements which morphine undergoes has earned for it, in the words of Sir Robert Robinson (23), the reputation of being "a star performer among molecular acrobats".

It is hoped that this article has shown that morphine, possibly to a greater extent than any other single natural product, has created extensive interest among organic chemists. Those chemists who have, in whole or in part, successfully attacked the problem of its synthesis, have been more than once rewarded, perhaps because of the elusiveness of the "star performer" with rich gifts of stereochemical good fortune by a merciful and bounteous Providence.

This article is dedicated to Dr. Lyndon Frederick Small whose work on opium alkaloids contributed in large measure to the author's interest in this field.



LXXII



LXXIII

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New Peruvian Legislation on Cocaine Manufacture

Republic of Peru, Ministry of Public Health and Social Welfare

Directorate-General of Public Health

SUPREME DECREE No. 81-"SP"

Whereas, by Legislative Decree No. 11444 the State has been made responsible for the industrialization of coca under the technical supervision of the Ministry of Public Health and Social Welfare,

And whereas article 1 of that decree provides that regulations shall be made for the manufacture of and trade in crude cocaine, pure cocaine, its salts and derivatives, to ensure the necessary technical control and better administrative supervision in accordance with the international conventions on "drugs",

The President of the Republic

Hereby decrees as follows:

Article 1. The manufacture of crude cocaine, pure cocaine and its salts and derivatives shall be the responsibility of the Fiscal Laboratories for the Industrialization of Coca and be supervised by a Board of Administration and Control over which the Director-General of Public Health shall preside and which shall be composed of the Director-General of the National Health and Social Welfare Fund, the Administrator-General of the Coca Monopoly, the head of the Division of Pharmacy, the head of the Department of Narcotics, the head of the Department of Mental Hygiene, the Director of Investigation and a representative of the Ministry of Finance.

Article 2. It shall be the duty of the Board of Administration and Control:

(*a*) To give initial approval to the draft annual budget, which shall be submitted to the Supreme Government through the Ministry of Finance and Commerce;

(*b*) To ensure the execution thereof;

(*c*) To approve the annual balance-sheet;

(*d*) To countersign the detailed annual inventory of the assets of the Administration under its charge;

(*e*) To scrutinize and approve before transmission to the Ministry of Finance and Commerce any expenditure relating to installations or to additions to the laboratories or their administrative budget;

(*f*) To authorize all supply, procurement and sales contracts;

(*g*) To supervise all bids and sales at auction;

(*h*) To ensure that the provisions of national and international narcotics control law relating to the manufacture of and trade in cocaine and its derivatives are strictly observed;

(*i*) To recommend to the Ministry of Public Health appointments to the technical and administrative staff of the organization;

(*j*) To check revenue and expenditure arising out of the industrialization;

(*k*) To submit an annual report on the Board's work.

Article 3. Cocaine hydrochloride may be manufactured only from crude cocaine paste prepared from coca leaf at the Fiscal Laboratories.

Cocaine hydrochloride from any source other than the Fiscal Laboratories shall be deemed to be contraband.

Article 4. Crude cocaine, pure cocaine and its salts shall be manufactured in mutually-independent establishments not connected with any other activity and directed by separate technical officers.

The Narcotics Contraband Department of the Directorate-General of Investigation shall permanently supervise production, ascertain the quantities prepared, and inspect stocks of alkaloids.

Article 5. The laboratory producing pure cocaine and its salts may not use crude cocaine, and the laboratory producing crude cocaine may not use coca leaves, in their respective preparations without the express leave of the Directorate-General of Public Health.

Article 6. The tax collection offices of the production centres shall use, for the coca leaves to be sent to the Fiscal Laboratories to which this Decree relates, and in accordance with the permits issued by the Directorate-General of Public Health, special books of transit notes of a different colour and shape from those at present used in commerce.

The transit notes shall contain the following particulars:

(*a*) Date and number of the permit or licence;

(*b*) Gross and net weight of the package, on the wrapping of which the names of the supplying firm and consignee and the place of destination shall be clearly marked;

(*c*) The source and quality of the leaves;

(*d*) The means of transport and route to be used, and the date of shipment;

(*e*) The date of expiry of the certificate (not more than fifteen days after the date of despatch).

Article 7. The Deposit and Consignment Office shall transmit immediately by telegraph to the Department of Narcotics full particulars of certificates issued.

The police of each area shall check by suitable countersignature the despatch certificates and transit notes issued by offices of the Tax Collection Department mentioned in the preceding article.

Article 8. Transit certificates shall bear a record, duly stamped and signed by the staff of the Tax Collection Department at the stations or check points on the prescribed route, of the time and date of the check, which shall in each case include verification of the particulars recorded on the certificate.

Article 9. Transport undertakings shall not despatch coca leaves without production of a certificate which shall be issued in each case by the Tax Collection Department of the Deposit and Consignment Office and on which they shall record the shipment of the consignment.

Article 10. Immediately upon arrival in this capital of a consignment of coca leaves for the aforesaid purposes, the Administration of the Fiscal Laboratories shall deliver to the Department of Narcotics the relevant transit certificate, which shall show the quantities of raw materials in the consignment.

The Narcotics Contraband Department of the Directorate-General of Investigation, Inspection and Identification shall keep a Register of Coca Producers of the Republic in which shall be recorded the area of cultivations and the quantity and quality of annual coca crops.

Station commandants of the Civil Guard shall transmit to the Directorate-General of Investigation, Inspection and Identification lists of coca producers and owners of land in their respective areas.

Article 11. The technical direction of the laboratories in which crude and pure cocaine is prepared shall be carried out by qualified chemists, to be appointed by the Ministry of Public Health on the recommendation of the Board of Administration and Control.

Article 12. In addition to their technical duties, officers engaged in the technical direction of crude and pure cocaine laboratories shall:

(*a*) Keep, in a book authorized by the Department of Narcotics, separate accounts of the movement of coca leaf, of crude cocaine, of pure cocaine and of its salts, with the date of each operation;

(*b*) Submit monthly to the Department of Narcotics a statement of these accounts, whether movement has occurred during the month or not;

(*c*) Obtain prior leave of the Department of Narcotics to use coca leaves in the manufacture of crude cocaine, and to use crude cocaine in the preparation of pure cocaine, its salts and derivatives; for which purpose the Department shall take for analysis samples, which shall be supplied for that purpose, of separate batches of the products prepared.

(*d*) Keep, in books previously authorized by the Department of Narcotics, stock registers of chemical solvents and products procured and used by the laboratories;

(*e*) Note in the appropriate register the quantity and source of the coca leaves used in each operation;

(*f*) Note the output of crude or pure cocaine from each batch processed, and the percentage of pure cocaine and total alkaloids obtained from crude cocaine in each batch processed;

(*g*) Number the containers of each batch and seal each container securely.

Article 13. The Fiscal Laboratories producing coca derivatives may not supply drugs or accept raw materials without the knowledge and express authority of the Directorate-General of Public Health.

Article 14. When preparation at the laboratories is suspended, the responsible technical officer shall have suitable seals placed on the extraction and processing equipment and shall report accordingly to the Directorate-General, and send also a stock statement of drugs, raw materials and other items.

Article 15. Crude cocaine and cocaine hydrochloride produced shall be deposited at the Ministry of Public Health on the tenth, twentieth and thirtieth days of each month or on the last working day before such days when they fall on holidays. Invoices therefor shall be compiled and attached to the monthly accounts, which shall be sent to the Ministry by the fifth day of the next month.

Article 16. Requests for permission to export or sell crude cocaine, pure cocaine or its salts shall be submitted in accordance with the rules in force. The documents relating to each case shall be accompanied by a copy of the chemical analysis of the product, certified by the Department of Narcotics.

Article 17. The products deposited at the Ministry of Public Health shall be in the charge of the head pharmacist of the Narcotics Laboratory of the Procurement, Production and Supply Division and the head of the Department of Narcotics of the Directorate-General of Public Health, who shall keep a receipt and issue a register for the products under their charge and shall submit a monthly stock statement to the Board of Administration.

Article 18. Any infringement of the provisions of this Decree shall be an offence at law punishable in accordance with the provisions in force.

Article 19. The products of the Fiscal Laboratories for the Industrialization of Coca, and all materials procured by them for production or trade, shall be exempted from all taxation.

Article 20. The Procurement, Production and Supply Division of the Directorate-General of the National Health and Social Welfare Fund of the Ministry of Public Health and Social Welfare shall provisionally defray the cost of procuring materials and installing the laboratories.

Article 21. The Board of Administration and Control shall propose to the Ministry of Public Health and Social Welfare such measures as it may deem likely to improve the work of the Fiscal Laboratories for the Industrialization of Coca.

Given at the Casa de Gobierno, Lima, on 11 June 1953.

(*Signed*) Manuel A. ODRIA
Luis N. SÁENZ
Emilio ROMERO

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SCIENTIFIC PUBLICATIONS ON NARCOTIC DRUGS FOR 1952

INTRODUCTION

The following bibliography has been prepared by the Secretariat and includes scientific publications on narcotic drugs which appeared during 1952, as well as a few which appeared earlier but could not, for various technical reasons, be included in the preceding lists published in No. 3 of volumes II, III and IV of the *Bulletin on Narcotics*. This bibliography has no claim to be complete, and information regarding books or articles not included in it would be gratefully received by the Division of Narcotic Drugs, Department of Social Affairs, United Nations Secretariat.

The bibliography has been arranged by subject in the following way:

Part I. General and reference works

Part II. Opium poppy, opium and drugs manufactured therefrom

A. Opium poppy and opium

B. Morphine

C. Other phenanthrene alkaloids and derivatives of opium (under the Conventions)

D. Other drugs and substances derived from the opium poppy

Part III. A. The coca leaf

B. Drugs manufactured from the coca leaf

Part IV. *Cannabis* and its derivatives

Part V. Synthetic drugs

A. General works

B. Pethidine and related compounds

C. Methadone and related compounds

D. Morphinan and morphine synthesis

Part VI. Addiction to narcotic drugs

Part VII. Miscellaneous

Under each heading, publications are arranged alphabetically by author. Due to the nature of the sources available to the Secretariat for preparing this bibliography, several titles are given in translation only. They are preceded by an asterisk.

Part I

GENERAL AND REFERENCE WORKS

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Part II

OPIUM POPPY, OPIUM AND DRUGS MANUFACTURED THEREFROM

A. Opium poppy and opium

A

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Part IV

CANNABIS AND ITS DERIVATIVES

Part V

SYNTHETIC DRUGS

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